Appropriate for the Protection of the Public Health: Why We Need Electronic Nicotine Delivery System Product Standards

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ABSTRACT

Combustible tobacco products (e.g., cigarettes and cigars) continue to be one of the leading causes of preventable disease, disability, and death in the United States. Despite over a century of understanding the harms of tobacco products, a combination of political, policy, and legal battles delayed federal tobacco product regulation until the passage of the 2009 Family Smoking Prevention and Tobacco Control Act. The Act created a new center within the U.S. Food and Drug Administration (FDA), the Center for Tobacco Products (CTP), responsible for reviewing and granting marketing authorization for tobacco products based upon a novel regulatory standard "Appropriate for the Protection of the Public Health" (the APPH standard). A novel legal standard for federal regulators, the APPH standard has never been interpreted by

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the judicial branch. CTP has struggled to interpret and apply it, especially as it relates to Electronic Nicotine Delivery Systems (ENDS products or e-cigarettes).

In December of 2022, the Reagan-Udall Foundation completed its third-party review of CTP's thirteen-year history and found multiple policy and operational gaps. Specifically, the report criticized CTP for a lack of transparency and timeliness in its approach to harm reduction (that is, promoting the use of tobacco products that are less dangerous than combustibles, such as smokeless tobacco and ENDS products). It repeatedly encouraged CTP to shift from a reactive to proactive state by, *inter alia*, publishing objective product standards for premarket authorization that would satisfy the statutory definition of "Appropriate for the Protection of the Public Health." This Article is the first to suggest such objective product standards for ENDS products. It does so by a thorough review of both scientific evidence and legal precedent in administrative law. Promulgation of objective product standards for ENDS products would enshrine harm reduction into the Appropriate for the Protection of the Public Health standard underlying tobacco regulation, providing regulatory clarity for advocates, industry, and policymakers.

I. INTRODUCTION

The regulation of Electronic Nicotine Delivery Systems (ENDS products) by the U.S. Food and Drug Administration's (FDA or the agency) Center for Tobacco Products (CTP) has been controversial. After lengthy delays in establishing its regulatory authority and receipt of approximately 6.5 million Premarket Tobacco Product Applications (PMTAs) for ENDS products, the agency did not issue its first marketing authorization order until October of 2021. This was shortly following a series of en masse marketing denial orders (MDOs) for approximately 55,000 flavored ENDS products and subsequently an MDO for all JUUL products (flavored and non-flavored) in June of 2022. These contentious decisions frustrated public health experts, current smokers, consumers, and product manufacturers who view ENDS products as an important tool to reduce the harms caused by cigarettes and other combustible forms of tobacco.[1] This frustration was compounded by the lack of transparency from the agency regarding the standards for authorization. Rather than publishing any public-facing objective cutoffs or official interpretation of scientific data, FDA has been issuing product-by-product adjudications on each application, several of which have been appealed in federal court. Meanwhile, the approximately 11,000 grandfathered combustible tobacco products that are (and will continue to be) readily available on the market,[2] with estimated domestic sales of 10.79 billion packs of cigarettes in 2020,[3] continue to cause preventable diseases and deaths in American smokers. Without proactive product standards for ENDS products, CTP is bypassing

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[1] David J. K. Balfour, Neal L. Benowitz, Suzanne M. Colby, Dorothy K. Hatsukami, Harry A. Lando, Scott J. Leischow, Caryn Lerman, Robin J. Mermelstein, Raymond Niaura, Kenneth A. Perkins, Ovide F. Pomerleau, Nancy A. Rigotti, Gary E. Swan, Kenneth E. Warner & Robert West, *Balancing Consideration of the Risks and Benefits of E-Cigarettes*, 111 AM. J. PUB. HEALTH 1661; 1661, 1667 (2021).

[2] U.S. FOOD & DRUG ADMIN., *Standalone Pre-Existing Tobacco Product Determinations*, https://www.accessdata.fda.gov/scripts/ctppx/ (last visited Apr. 3, 2023) (selecting for cigarettes, cigars, roll-your-own, and pipe tobacco product types).

[3] Lungile Nkosi, Satomi Odani & Israel T. Agaku, *20-Year Trends in Tobacco Sales and Self-Reported Tobacco Use in the United States, 2000–2020*, 19 PREVENTING CHRONIC DISEASE, at Table 1 (2022), http://dx.doi.org/10.5888/pcd19.210435.

an opportunity to establish objective parameters for a less harmful product for those addicted to combustible tobacco and achieve public health goals by shifting the population of combustible tobacco users down the tobacco risk continuum.

This article proceeds in four parts. First, ENDS products are introduced by comparison to their historical counterpart, combustible tobacco products, with particular attention to medical harms and prior public health efforts aimed at reducing combustible tobacco use. After showing that these efforts have resulted in a plateau in the number of current users able to achieve cessation, Part III discusses the legal history of federal regulation of tobacco products and ENDS products, specifically. It highlights how the language of the Family Smoking Prevention and Tobacco Control Act (TCA) led to challenges with the timeliness and transparency of FDA's early attempts to regulate ENDS products. It subsequently reviews the administrative law procedures available to FDA for making substantive rules such as would be required for the promulgation of product standards as a binding norm for future product marketing authorization.

Part IV delves into scientific and public health literature regarding the harm reduction potential of ENDS products. It focuses on both tangible aspects of ENDS products that are amenable to numeric, bright line cutoffs, as well as broader public health implications amenable to population (and sub-population) level studies regarding use patterns and motivation for use. Finally, it concludes in Part V by arguing that, based on a combination of FDA's prior authorization decisions and publicly available scientific studies, product standards for ENDS products can and should be established. Doing so, even at this juncture, will send notice to ENDS products users, makers, and public health officials about the relative risks and benefits of these products relative to combustible tobacco.

This approach was recommended by the Reagan-Udall Foundation after conducting its third-party review of the thirteen-year history of CTP in December of 2022.[4] The report highlighted how CTP has sent mixed messages regarding its approach to harm reduction vis-à-vis ENDS product regulation and suggests that promulgating objective parameters that could serve as product standards for marketing authorization would help the center transition from a reactive to proactive regulatory policy. We close by arguing that regulators must take into account the continuum of risk in the regulation of ENDS products. Harm reduction for current combustible tobacco users must be counterbalanced by new tobacco-derived product use, including considering potential youth uptake. This is in addition to evaluating the specific, submitted scientific and clinical data in each PMTA. Promulgating ENDS product standards would provide regulatory and scientific clarity, while effectively enshrining in practice a harm reduction framework into the Appropriate for the Protection of the Public Health standard of the TCA.

[4] REAGAN-UDALL FOUND., OPERATIONAL EVALUATION OF CERTAIN COMPONENTS OF FDA'S TOBACCO PROGRAM (Dec. 2022), https://reaganudall.org/sites/default/files/2022-12/Tobacco%20report%20210pm.pdf [hereinafter REAGAN-UDALL REPORT].

II. THE CONTINUUM OF RISK FOR TOBACCO PRODUCTS

A. Harms of Combustible Tobacco

Combustible tobacco products (i.e., those that are lit on fire for consumption) have a long history in North America that has been fraught with public health controversies. Cigarettes became the predominant form of tobacco in the early 20th Century after the advent of the automated cigarette rolling machine as well as the proliferation of direct-to-consumer advertising.[5] After decades of battling misinformation from makers of tobacco products and even some medical professionals—including physicians[6]—the harmful health effects of combustible tobacco products began to come to light in the early-to-mid-1900's, culminating in the landmark 1964 U.S. Surgeon General's Report on Smoking and Health.[7] This report ushered in the modern era of tobacco control, as it led to the first Surgeon General Warning Labels, as well as antismoking public health communication campaigns.[8]

It is difficult to overstate the harmful health effects of combustible tobacco products. With over 20 million deaths in the United States in the past fifty years, the death toll from tobacco is over ten-fold higher than the number of American casualties in all wars fought in U.S. history.[9] To date, use of combustible tobacco products has been shown to cause an increase in coronary artery disease (with or without myocardial infarction or heart attack), congestive heart failure, stroke, peripheral arterial and venous vascular diseases, deep vein thrombosis, pulmonary embolism, chronic obstructive lung disease, and multiple forms of cancer (including carcinomas of the lung, bladder, head/neck, esophagus, kidney, cervix, liver, as well as certain forms of leukemia).[10] To compare with a recent public health crisis with significant

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[5] ALLAN M. BRANDT, THE CIGARETTE CENTURY: THE RISE, FALL, AND DEADLY PERSISTENCE OF THE PRODUCT THAT DEFINED AMERICA 27–30, 75 (Basic Books 2007).

[6] Martha N. Gardner & Allan M. Brandt, *"The Doctors' Choice Is America's Choice": The Physician in US Cigarette Advertisements, 1930–1953*, 96 AM. J. PUB. HEALTH 222, 222–32 (2006).

[7] PUB. HEALTH SERV., U.S. DEP'T OF HEALTH & HUMAN SERVS., SMOKING AND HEALTH: REPORT OF THE ADVISORY COMMITTEE TO THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE (1964), https://www.govinfo.gov/content/pkg/GPO-SMOKINGANDHEALTH/pdf/GPO-SMOKINGANDHEALTH.pdf.

[8] K. Michael Cummings & Robert N. Proctor, *The Changing Public Image of Smoking in the United States: 1964–2014*, 23 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 32, 32–33 (2014); FED. TRADE COMM'N, REPORT TO CONGRESS PURSUANT TO THE FEDERAL CIGARETTE LABELING AND ADVERTISING ACT 4–30 (June 30, 1967).

[9] OFF. OF THE SURGEON GEN., PUB. HEALTH SERV., U.S. DEP'T OF HEALTH & HUM. SERVS., THE HEALTH CONSEQUENCES OF SMOKING 50 YEARS OF PROGRESS (2014), https://www.ncbi.nlm.nih.gov/books/NBK179276/pdf/Bookshelf_NBK179276.pdf [hereinafter 2014 SURGEON GENERAL REPORT]; *Number of Military Fatalities in All Major Wars Involving the United States from 1775 to 2023*, STATISTA, https://www.statista.com/statistics/1009819/total-us-military-fatalities-in-american-wars-1775-present/ (last visited June 8, 2023) (sum of the included data is 1,304,702).

[10] *Smoking & Tobacco Use: Diseases and Death*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/diseases-and-death.html (last visited Mar. 9, 2023); Jay H. Lubin, David Couper, Pamela L. Lutsey, Mark Woodward, Hiroshi Yatsuya & Rachel R. Huxley, *Risk of Cardiovascular Disease from Cumulative Cigarette Use and the Impact of Smoking Intensity*, 27 EPIDEMIOLOGY 395, 395–404 (2016); Carlos Iribarren, Irene S. Tekawa, Stephen Sidney & Gary D. Friedman, *Effect of Cigar Smoking on the Risk of Cardiovascular Disease, Chronic Obstructive Pulmonary Disease, and Cancer in Men*, 340 NEW ENG. J. MED. 1773, 1773–79 (1999); Niki Katsiki, S.K. Papadopoulou, A.I. Fachantidou & D.P. Mikhailidis, *Smoking and Vascular Risk: Are All Forms of Smoking Harmful to All Types of Vascular Disease?*, 127 PUB. HEALTH 435, 435–38 (2013); Julian Peto, *Cancer*

morbidity and mortality: COVID-19 caused approximately the same number of deaths as the use of combustible tobacco.[11] The life expectancy of smokers (i.e., users of combustible tobacco products) is at least ten years shorter than that of non-smokers,[12] and smokers have at least a 72% higher mortality risk than non-smokers.[13]

In 2014, the Office of the Surgeon General, which one of the authors headed at the time, released the 50th Anniversary Report on Smoking and Health.[14] This report updated the public on the recognized health hazards of smoking and outlined the overall risk to national morbidity and mortality due to smoking. Specifically, it found that 8 million lives had been saved since 1964 based on early public health efforts aimed at smoking prevention.[15] The 50th Anniversary Report also highlighted several public health measures instituted over the past five decades and their impact on smoking rates and public health generally.[16] These efforts are discussed in more detail *infra* in Section II.B. The 50th Anniversary Report emphasized the historical trends and information on how tobacco use shifted over the previous fifty years, presented new findings on the health effects of smoking, and announced a call to action to end the continuing tobacco use epidemic.

Bringing tobacco products under federal regulatory control was an ardent task. In 1997, then-FDA commissioner Dr. David Kessler attempted to regulate nicotine as a drug and cigarettes as medical devices (as they "deliver" nicotine).[17] However, this approach was thwarted by the U.S. Supreme Court in 2000 when it determined in a 5–4 ruling that FDA lacked statutory authority to regulate tobacco products.[18] Contemporaneously, Attorneys General from forty-six states sued the four largest tobacco manufacturers to recover their states' Medicaid expenditures for treating tobacco-related illnesses on the basis of systematic fraud.[19] These efforts ultimately

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Epidemiology in the Last Century and the Next Decade, 411 NATURE 390, 393 (2001); Prabhat Jha, Chinthanie Ramasundarahettige, Victoria Landsman, Brian Rostron, Michael Thun, Robert N. Anderson, Tim McAfee & Richard Peto, *21st Century Hazards of Smoking and Benefits of Cessation in the United States*, 368 NEW ENG. J. MED. 341, 341–49 (2013).

[11] *Compare Smoking & Tobacco Use*, *supra* note 10 ("Cigarette smoking is responsible for more than 480,000 deaths per year") *with Coronavirus Resource Center*, JOHNS HOPKINS UNIV. OF MED., https://coronavirus.jhu.edu/ (last visited Mar. 10, 2023) (1.12 million deaths attributed to COVID-19 as of March 10, 2023).

[12] Nancy A. Rigotti, *Patterns of Tobacco Use* (Jan. 21, 2022), https://www.uptodate.com/contents/patterns-of-tobacco-use. *See also Smoking & Tobacco Use: Tobacco-Related Mortality*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm (last visited Mar. 10, 2023).

[13] Maki Inoue-Choi, Timothy S. McNeel, Patricia Hartge, Neil E. Caporaso, Barry I. Graubard & Neal D. Freedman, *Non-Daily Cigarette Smokers, Mortality Risks in the United States*, 56 AM. J. OF PREVENTATIVE MED. 27, 27–35 (2019) (noting that lifelong non-daily smokers who had never smoked daily still had a 72% higher mortality risk compared to lifelong non-smokers).

[14] 2014 SURGEON GENERAL REPORT, *supra* note 9, at 865.

[15] *Id.* at 856.

[16] *Id.* at 15–33; 771–826.

[17] *See* David A. Kessler, Philip S. Barnett, Ann Witt, Mitchell R. Zeller, Jerold R. Mande, & William B. Schultz, *The Legal and Scientific Basis for FDA's Assertion of Jurisdiction Over Cigarettes and Smokeless Tobacco*, 277 JAMA 405 (1997).

[18] U.S. Food & Drug Admin. v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000).

[19] *See* Steven A. Schroeder, *Tobacco Control in the Wake of the 1998 Master Settlement Agreement*, 350 NEW ENG. J. MED. 293, 293 (2004).

led to a $206 billion settlement between states and tobacco companies called the Tobacco Master Settlement Agreement ("Settlement"), which, *inter alia*, created the American Legacy Foundation for public education and other tobacco control activities.[20] For a variety of reasons, ranging from companion federal legislation failing on the Senate floor[21] to state governments shifting money from the Settlement to non-tobacco-related expenditures, the Settlement did not result in a uniform national regulatory system for combustible tobacco products.[22]

B. Policy Efforts to Decrease Combustible Tobacco Use

More recent efforts at tobacco regulations began with increasing sales taxes on tobacco products, which have been implemented on the federal, state, and local levels.[23] Initially considered purely revenue-generating taxes, public health leaders now consider these "sin taxes" as one, if not the most important, regulatory tool to decrease combustible tobacco use.[24] Other regulatory efforts have been aimed at limiting advertisements that are either false/misleading or target specific populations, such as teenagers. Given the tobacco industry's history of propagating misinformation and using deceptive tactics,[25] the Federal Trade Commission (FTC) closely regulates the marketing and point-of-sale practices of tobacco makers.[26] Additionally, FTC ensures that statutorily required Surgeon General Warning labels that describe the health hazards of the products are displayed on all packaging.[27]

Of note, these efforts were (and still are) implemented via state/local law or through FTC oversight of advertising laws, rather than through direct FDA product regulation and FDA marketing oversight. Further action occurred at the state and municipal level, as state and local governments implemented Clean Indoor Air laws prohibiting smoking indoors. Beginning with Minnesota in 1975, all fifty states and the District of Columbia currently have restrictions on smoking in at least some indoor spaces in addition to approximately 2,600 municipal laws.[28] These laws have led to a decrease in the number of smokers within the respective jurisdictions by approximately 34%

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[20] *Id.* at 294.

[21] Universal Tobacco Settlement Act, S.1415, 105th Cong. (1998).

[22] *See* Schroeder, *supra* note 19, at 296–300.

[23] COMM. ON PREVENTING NICOTINE ADDICTION IN CHILDREN & YOUTHS, INST. OF MED., GROWING UP TOBACCO FREE: PREVENTING NICOTINE ADDICTION IN CHILDREN AND YOUTHS 177–96 (Barbara S. Lynch & Richard J. Bonnie eds., 1994).

[24] Frank J. Chaloupka, Ayda Yurekli & Geoffrey T. Fong, *Tobacco Taxes as a Tobacco Control Strategy*, 21 TOBACCO CONTROL 172, 172–80 (2012); *World Health Organization (WHO): Framework Convention on Tobacco Control*, WORLD HEALTH ORG. 7–8 (2003), https://www.cambridge.org/core/journals/international-legal-materials/article/abs/world-health-organization-who-framework-convention-on-tobacco-control/2735AF0E18B517CFA95A18E96FB22C35.

[25] Richard D. Hurt, Jon O. Ebbert, Monique E. Muggli, Nikki J. Lockhart & Channing R. Robertson, *Open Doorway to Truth: Legacy of the Minnesota Tobacco Trial*, 84 MAYO CLINIC PROC. 446, 446–48 (2009) (highlighting the internal business documents from the tobacco industry released publicly through the Master Settlement Agreement that included marketing strategies targeting youth and misrepresenting the known harms of combustible tobacco use).

[26] PETER C. WARD, FEDERAL TRADE COMMISSION: LAW, PRACTICE AND PROCEDURE 10-4 (2022).

[27] Federal Cigarette Labeling and Advertising Act, 15 U.S.C. §§ 1331-1340; 21 U.S.C. § 387c.

[28] Michael P. Eriksen & Rebecca L. Cerak, *The Diffusion and Impact of Clean Indoor Air Laws*, 29 ANN. REV. PUB. HEALTH 171, 174–76 (2008).

(Odds Ratio 0.66),[29] the amount of secondhand smoke exposure in the population,[30] and the amount of consumption by active smokers (-2.36 cigarettes/day).[31] Moreover, these Clean Indoor Air laws appear to benefit all socioeconomic and racial/ethnic groups equally.[32]

Other policy efforts targeted the age for the sale of tobacco products. Passed as part of a larger spending bill on December 20, 2019,[33] the new age requirement, colloquially called "Tobacco 21 Act," went into effect that same day, raising the minimum age for the sale of tobacco products by retailers and other entities from eighteen to twenty-one. It did not contain any grandfathering provisions for those persons already aged eighteen, nineteen, or twenty (i.e., those who were able to purchase tobacco products before the new law). Moreover, there were no exceptions made for active members of the military who were less than twenty-one years of age. The law made the sale (but not purchase) illegal to those under twenty-one, making retailers rather than consumers the intended target.[34] Striking a delicate balance between state and federal power, the Tobacco 21 Act did not require states to change their laws regarding age restrictions, but it did require them to help enforce the law by conducting random, unannounced inspections to ensure that retailers do not sell tobacco products to individuals under the age of twenty-one and annually reporting to the Secretary of the U.S. Department of Health and Human Services: A) the activities carried out by the states to ensure that retailers do not sell tobacco products to individuals under the age of twenty-one; B) the extent of success the state has achieved in ensuring that retailers do not sell tobacco products to individuals under the age of twenty-one; and C) the strategies to be utilized by the state to ensure that retailers do not sell tobacco products to individuals under the age of twenty-one.[35] The penalty for a state failing to conduct these enforcement duties is 10% of its federal funding for state-run substance abuse programs.[36]

The aforementioned policy efforts, to date, have been successful insofar as the prevalence of cigarette smoking has declined from 42% of the adult population in

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[29] Alexis Dinno & Stanton Glantz, *Tobacco Control Policies Are Egalitarian: A Vulnerabilities Perspective on Clean Indoor Air Laws, Cigarette Prices, and Tobacco Use Disparities*, 68 SOC. SCI. & MED. 1439, 1439 (2009).

[30] Eriksen & Cerak, *supra* note 28, at 177–79.

[31] Dinno & Glantz, *supra* note 29, at 1439. *See also* Eriksen & Cerak, *supra* note 28, at 179 (stating "Levy and Friend estimate that comprehensive public clean indoor air laws could reduce cigarette consumption and smoking prevalence rates by 10%. Fichtenberg & Glantz estimate that smoke-free workplaces result in reductions in smoking prevalence and fewer cigarettes smoked per day for continuing smokers and that if all workplaces were smoke-free, per capita consumption would drop by 4.5%. Researchers found that strong smoke-free restaurant policies were associated with adult smokers' perceptions that smoking was socially unacceptable, thus these smokers were three times more likely to attempt to quit.").

[32] Dinno & Glantz, *supra* note 29, at 1439.

[33] Further Consolidated Appropriations Act, 2020, Div. N., Title I, §§ 603-604, Pub. L. No. 116-94, 133 Stat. 2534, 3123–27 (2019).

[34] *Id.* § 603(a)(2).

[35] *Id.* § 604(a)(4).

[36] *Id.* § 604(a)(5).

1965[37] to 12.5% in 2020.[38] A similar trend can be seen in the rates of tobacco uptake by new users: past thirty-day smoking rates among grade eight, ten, and twelve students combined dropped from 28.3% in 1997 to 3.7% in 2019.[39] This is a significant decline from a late 1950's survey commissioned by the cigarette industry, which found that in 1959, 56% of high school students and 75% of college students were regular smokers.[40] Unfortunately, quit rates have plateaued over the past few decades despite increased efforts in community and medical tobacco cessation programs, clinician-supervised pharmacotherapy and consumer-directed nicotine replacement therapy,[41] education, increased taxes, and updated warning labels.[42] This trend suggests that overall smoking rates over the past few decades have been primarily driven by the declining entrance rate of new smokers, particularly amongst teens and young adults. However, smoking cessation rates amongst already active smokers have reached a point of diminishing returns. Or put another way: public health efforts to prevent people from smoking in the first place have been far more successful than those aimed at cessation for current smokers.[43]

Recent efforts have targeted new levers for tobacco control: product regulation. The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act or TCA)

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[37] Gary A. Giovino, M. W. Schooley, B. P. Zhu, J. H. Chrismon, S. L. Tomar, J. P. Peddicord, R. K. Merritt, C. G. Husten & M. P. Eriksen, *Surveillance for Selected Tobacco-Use Behaviors—United States, 1900–1994*, 43 MORBIDITY & MORTALITY WKLY. REP. 1, at 5 (1994).

[38] Monica E. Cornelius, Caitlin G. Loretan, Teresa W. Wang, Ahmed Jamal & David M. Homa, *Tobacco Product Use Among Adults—United States, 2020*, 71 MORBIDITY & MORTALITY WKLY. REP. 397, 397 (2022). *See also* Kenneth Michael Cummings, Scott Ballin & David Sweanor, *The Past is Not the Future in Tobacco Control*, 140 PREVENTIVE MED. 2 (2020) (reviewing the history of tobacco control).

[39] Richard A Miech, J. E. Schulenberg, L.D. Johnston, J.G. Bachman, P. M. O'Malley & M. E. Patrick, *National Adolescent Drug Trends in 2019: Findings Released*, Table 7, https://monitoringthefuture.org/data/19data.html (last visited Apr. 4, 2023).

[40] WILLIAM ESTY CO., INC., THE YOUTH RESEARCH INSTITUTE STUDY REGARDING CIGARETTE SMOKING AMONG 7,521 HIGH SCHOOL AND COLLEGE STUDENTS IN 80 CITIES THROUGHOUT THE UNITED STATES, OCTOBER–NOVEMBER, 1959, SUMMARY OF FINDINGS, Table 1 (1959), https://www.industrydocuments.ucsf.edu/docs/qrgj0045 (last visited Apr. 5, 2023).

[41] Examples of medical therapy for tobacco use disorder (prescription and/or over-the-counter) include nicotine replacement therapy (NRT) (e.g., gum, lozenges, patches, inhalers, and nasal sprays), varenicline, and bupropion. NRT, as a class, increases the rates of smoking cessation by approximately 55% when compared to placebo. Lindsay F. Stead, Rafael Perera, Chris Bullen, David Mant, Jamie Hartmann-Boyce, Kate Cahill & Tim Lancaster, *Nicotine Replacement Therapy for Smoking Cessation*, COCHRANE DATABASE SYSTEMATIC REVS. No. 11, CD000146 (2012). Varenicline is 122% more effective than placebo. Kate Cahill, Nicola Lindson-Hawley, Kyla H. Thomas, Thomas R. Fanshawe & Tim Lancaster, *Nicotine Receptor Partial Agonists for Smoking Cessation*, COCHRANE DATABASE SYSTEMATIC REVS. No. 5, CD006103 (2016). Bupropion is 64% more effective than placebo. Seth Howes, Jamie Hartmann-Boyce, Jonathan Livingstone-Banks, Bosun Hong & Nicola Lindson, *Antidepressants for Smoking Cessation*, COCHRANE DATABASE SYSTEMATIC REVS. No. 4, CD000031 (2020). However, these data are limited to the setting of randomized controlled trials in which the participants show a willingness to quit. In practice, data from the National Health Interview Surveys reflected that in 2010, 68.8% of smokers wanted to stop smoking, 52.4% had made a quit attempt in the past year, 31.7% had used counseling and/or medications when attempting to quit, and only 6.2% had successfully quit. Ctrs. for Disease Control & Prevention, *Quitting Smoking Among Adults—United States, 2001–2010*, 60 MORBIDITY & MORTALITY WKLY. REP. 1513 (2011).

[42] Cummings et al., *supra* note 38, at 2–7 (discussing the plateauing quit rates).

[43] *Id.* (comparing the impact of efforts to prevent smoking initiation to efforts to promote cessation).

of 2009[44] was the first federal law that explicitly authorized FDA to regulate the manufacture, sale, and distribution of tobacco products. Passed with a 79–17 vote in the Senate and a 307–97 vote in the House and signed into law by President Obama,[45] the law established a new center within FDA called the Center for Tobacco Products (CTP) focused on tobacco products. Additionally, the law instituted a new standard for authorization (rather than "approval") that departed from the "safety and efficacy" or risk/benefit standards commonly applied to drugs and medical devices.[46] Rather, it required CTP to regulate tobacco products in ways that are "appropriate for the protection of the public health," or the APPH standard,[47] an authorization standard that was novel in the landscape of federal regulatory powers and had never been subject to judicial interpretation.[48] The statute directs CTP to make its determinations based on consideration of three elements:

> [1] the scientific evidence concerning the risks and benefits to the population as a whole, including users and nonusers of tobacco products . . . ; [2] the increased or decreased likelihood that existing users of tobacco products will stop using such products; and [3] the increased or decreased likelihood that those who do not use tobacco products will start using such products.[49]

The TCA allowed combustible and non-combustible products that existed on the market prior to February 15, 2007 ("grandfathered tobacco products" or "pre-existing tobacco products") to remain on the market.[50] Any new products or modifications to existing products must be authorized by CTP via either a showing of substantial equivalence (SE) to a pre-existing tobacco product or a tobacco product previously determined to be substantially equivalent[51] or via a Premarket Tobacco Product Application (PMTA) for new tobacco products.[52] In general, the PMTA pathway is

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[44] The Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, 123 Stat. 1776 (2009).

[45] H.R.1256—Family Smoking Prevention and Tobacco Control Act: All Actions, https://www.congress.gov/bill/111th-congress/house-bill/1256/all-actions?overview=closed#tabs (last visited Apr. 13, 2023).

[46] Mitchell Zeller, *Three Years Later: An assessment of the Implementation of the Family Smoking Prevention and Tobacco Control Act*, 21 TOBACCO CONTROL 453, 453 (2012).

[47] FDCA § 907(a)(3)(B)(i), 21 U.S.C. § 387g(3)(B)(i).

[48] *See generally* Eric N. Lindblom, *What Is Appropriate for the Protection of the Public Health Under the US Tobacco Control Act?*, 74 FOOD & DRUG L. J. 523 (2019); Ricardo Carvajal, David Clissold & Jeffrey Shapiro, *The Family Smoking Prevention and Tobacco Control Act, An Overview*, 64 FOOD & DRUG L.J. 717, 722–23 (2009).

[49] 21 U.S.C. § 387j(c)(4).

[50] *Pre-Existing Tobacco Products*, U.S. FOOD & DRUG ADMIN. (June 15, 2023), https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/pre-existing-tobacco-products#:~:text=In%20August%202022%2C%20FDA%20updated,as%20of%20February%2015%2C%202007 (last accessed June 8, 2023).

[51] FDCA § 905(j), 21 U.S.C. § 387e(j). Under § 387e(j)(3), products with a permissible modification consisting of adding or deleting an additive (or increasing or decreasing its quantity) may be exempted from the substantial equivalence authorization pathway.

[52] FDCA § 910(a)(2).

the more stringent authorization pathway.[53] As discussed in Part II, CTP did not define ENDS products as tobacco products subject to regulation until May 2016,[54] by which point any ENDS product that was commercially available prior to February 2007 was no longer physically available for an SE application.[55] Consequentially, ENDS products have had to seek marketing authorization via the rigorous PMTA pathway while many currently marketed combustible tobacco products are not subject to premarket application review requirements, so long as they were available prior to February 2007. Of note, the TCA gave FDA an explicit 180-day deadline for reaching an administrative decision on each PMTA,[56] longer than FDA's average review period for medical devices through the 510(k) pathway (108–124 days between 2018–2022)[57] and the same as FDA's statutory deadline for review of new drug applications.[58]

C. The Rise of ENDS Products

A patent describing the concept of an electronic inhalation device was issued as early as 1930,[59] and mass produced ENDS products had some notable false starts in the late 1990's (such as Premier and Eclipse),[60] with the product class in general not becoming available for purchase in the United States until about 2006.[61] The subsequent years saw a proliferation of varying ENDS products, including, but not limited to, e-cigarettes, vaporizers, vape pens, dab pens, dab rigs, tanks, mods, and mod-pods.[62] All of these products deliver nicotine via heating and aerosolization, rather than via combustion.[63] As the sales of ENDS products rose, they became particularly popular amongst younger users: between 2011 and 2018, the percentage

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[53] *See generally* Eric N. Lindblom, *The Tobacco Control Act's PMTA & MRTP Provisions Mean to Protect the USA from Any New Tobacco Products That Will Not Reduce Health Harms—But FDA Isn't Cooperating*, 23 J. HEALTH CARE L. & POL'Y 121, 136–37 (2020).

[54] Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products, 81 Fed. Reg. 28,974, 28,976 (May 10, 2016) (codified at 21 C.F.R. Part 1100) ("Deeming Rule").

[55] Todd A. Harrison, *FDA Issues Final Deeming Rule; E-Cigarettes, Vapor Products, and Cigars Among Products to be Regulated by the Agency for the First Time*, VENABLE (May 5, 2016), https://www.venable.com/insights/publications/2016/05/fda-issues-final-deeming-rule-ecigarettes-vapor-pr.

[56] FDCA § 910(c)(2)(A).

[57] PERFORMANCE REPORT TO CONGRESS: MEDICAL DEVICE USER FEE AMENDMENTS—FY 2022, U.S. FOOD & DRUG ADMIN. 9 (2022), https://www.fda.gov/media/167825/download.

[58] Audrey L. Gassman, Christine P. Nguyen & Hylton V. Joffe, *FDA Regulation of Prescription Drugs*, 376 NEW ENG. J. MED 674, 675 (2017); 21 U.S.C. § 355(c)(1); 21 C.F.R. § 314.101(a)(2).

[59] U.S. Patent No. 1,775,947-A (filed May 3, 1927) (issued Sept. 16, 1930).

[60] Jack E. Henningfield & John Slade, *Tobacco Product Regulation: Context and Issues*, 53 FOOD & DRUG L. J. 43, 56–57(1998) (discussing Premier and Eclipse products, the former of which was pulled after a few months of consumer testing in St. Louis and Phoenix due, in part, to how easily the device was able to be repurposed as a crack cocaine delivery system).

[61] *Historical Timeline of Vaping & Electronic Cigarettes*, CONSUMER ADVOCATES FOR SMOKE-FREE ALTERNATIVES ASS'N, https://casaa.org/education/vaping/historical-timeline-of-electronic-cigarettes/ (noting the first import ruling locatable in the U.S. Customs and Border Protection website database is dated August 22, 2006. NY M85579).

[62] CTRS. FOR DISEASE CONTROL & PREVENTION, E-CIGARETTE, OR VAPING, PRODUCTS VISUAL DICTIONARY v, vii (Dec. 13, 2019), https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/ecigarette-or-vaping-products-visual-dictionary-508.pdf.

[63] *Id.* at 8, 14, 17.

of high school students who had used an ENDS product within the last thirty days jumped from 1.5% to 20.8%.[64] In 2016, the Surgeon General issued a report on e-cigarette use among youth and young adults that highlighted concerns that ENDS product use would beget use of other, more harmful forms of tobacco and other substances in this vulnerable population.[65] The National Youth Tobacco Survey (NYTS) revealed that approximately 2.5 million U.S. youth used an ENDS product at least once in the past thirty days in 2021 (13.4% of high school students and 4.0% of middle school students),[66] which had declined from their peaks in 2019 (27.5% and 10.5%, respectively).[67] However, due to changes in survey methodology necessitated by the COVID pandemic, public health researchers have hesitated to compare data from the 2021 NYTS to prior years, making it difficult to determine whether the trend of declining rates from 2019 to 2020 to 2021 continued,[68] an important question to those monitoring the success of the impact of raising the legal age of purchase from eighteen to twenty-one, which took effect in December of 2019.[69]

Contemporaneously, a body of research began strengthening the proposition that ENDS products were less harmful than combustible alternatives. The largest prospective cohort study, ongoing since 2011, found that consumers who exclusively used ENDS products had approximately 34% less incidence of all cardiovascular disease compared to those who exclusively used combustible products.[70] However, in-human studies have also shown that ENDS products can cause potentially deleterious physiologic changes, such as increased oxidative stress, vascular endothelial damage and dysfunction, changes in vascular tone, altered alveolar immunohistology, and increased platelet activation.[71] When Marques et al. reviewed all in-human studies

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[64] Andrea S. Gentzke, MeLisa Creamer, Karen A. Cullen, Bridget K. Ambrose, Gordon Willis, Ahmed Jamal & Brian A. King, *Vital Signs: Tobacco Product Use Among Middle and High School Students—United States, 2011–2018*, 68 MORBIDITY & MORTALITY WKLY. REP. 157, 160 (Feb. 15, 2019), https://www.cdc.gov/mmwr/volumes/68/wr/pdfs/mm6806e1-H.pdf.

[65] OFF. OF THE SURGEON GEN., PUB. HEALTH SERV., U.S. DEP'T OF HEALTH & HUM. SERVS., E-CIGARETTE USE AMONG YOUTH AND YOUNG ADULTS: A REPORT OF THE SURGEON GENERAL (2016), https://www.cdc.gov/tobacco/data_statistics/sgr/e-cigarettes/pdfs/2016_sgr_entire_report_508.pdf [hereinafter 2016 SURGEON GENERAL REPORT].

[66] Andrea S. Gentzke, Teresa W. Wang, Monica Cornelius, Eunice Park-Lee, Chunfeng Ren, Michael D. Sawdey, Karen A. Cullen, Caitlin Loretan, Ahmed Jamal & David M. Homa, *Tobacco Product Use and Associated Factors Among Middle and High School Students—National Youth Tobacco Survey, United States, 2021*, 71 MORBIDITY & MORTALITY WKLY. REP. 1, 1 (Mar. 11, 2022).

[67] Teresa W. Wang, Linda J. Neff, Eunice Park-Lee, Chunfeng Ren, Karen A. Cullen & Brian A. King, *E-Cigarette Use Among Middle and High School Students—United States*, *2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 1310, 1310 (Sept. 18, 2020), https://www.cdc.gov/mmwr/volumes/69/wr/mm6937e1.htm.

[68] Gentzke et al., *supra* note 66, at 13.

[69] Further Consolidated Appropriations Act, 2020, Div. N., Title I, §§ 603-604, Pub. L. No. 116-94, 133 Stat. 2534, 3123–27 (2019).

[70] Jonathan B. Berlowitz, Wubin Xie, Alyssa F. Harlow, Naomi M. Hamburg, Michael J. Blaha, Aruni Bhatnagar, Emelia J. Benjamin & Andrew C. Stokes, *E-Cigarette Use and Risk of Cardiovascular Disease, A Longitudinal Analysis of the PATH Study (2013–2019)*, 145 CIRCULATION 1557, 1557–58 (2022).

[71] Maciej L. Goniewicz, Danielle M. Smith, Kathryn C. Edwards, Benjamin C. Blount, Kathleen L. Caldwell, Jun Feng, Lanqing Wang, Carol Christensen, Bridget Ambrose, Nicolette Borek, Dana van Bemmel, Karen Konkel, Gladys Erives, Cassandra A. Stanton, Elizabeth Lambert, Heather L. Kimmel, Dorothy Hatsukami, Stephen S. Hecht, Raymond S. Niaura, Mark Travers, Charles Lawrence & Andrew J. Hyland, *Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes*, JAMA NETWORK OPEN, Dec. 14, 2018, at 1–2 (finding that exclusive e-cigarette users showed

comparing ENDS users to cigarette users or non-users in 2021, the authors concluded that ENDS products, while not free from hazardous effects, seem to be less toxic than tobacco smoking.[72] The need for a less harmful alternative is immense: in 2020, 79.6% of adult tobacco product users consumed combustible products.[73] Indeed, a recent public health model estimates that 1.8 million premature smoking- and vaping-attributable deaths could be prevented by 2060 based on the 2021 rates of use of ENDS products, particularly as a substitution for combustibles products.[74] Initially controversial, there has been a growing recognition that nicotine-containing products

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10% to 98% significantly lower concentrations of biomarkers of exposure, including tobacco specific nitrosamines, polycyclic aromatic hydrocarbons, most volatile organic compounds (VOCs), and nicotine, compared with exclusive cigarette smokers; concentrations were comparable for metals and three VOCs); Pawel Lorkiewicz, Daniel W. Riggs, Rachel J. Keith, Daniel J. Conklin, Zhengzhi Xie, Saurin Sutaria, Blake Lynch, Sanjay Srivastava & Aruni Bhatnagar, *Comparison of Urinary Biomarkers of Exposure in Humans Using Electronic Cigarettes, Combustible Cigarettes, and Smokeless Tobacco*, 21 NICOTINE & TOBACCO RSCH. 1228, 1228 (2019) (finding combustible use results in exposure to a range of VOCs at concentrations higher than those observed with other products, and first generation e-cigarette use is associated with elevated levels of N,N-dimethylformamide and xylene metabolites); Roberto Carnevale, Sebastiano Sciarretta, Francesco Violi, Cristina Nocella, Lorenzo Loffredo, Ludovica Perri, Mariangela Peruzzi, Antonino G. M. Marullo, Elena De Falco, Isotta Chimenti, Valentina Valenti, Giuseppe Biondi-Zoccai & Giacomo Frati, *Acute Impact of Tobacco vs Electronic Cigarette Smoking on Oxidative Stress and Vascular Function*, 150 CHEST 606 (2016) (finding both e-cigarettes and traditional cigarettes led to a significant increase in the levels of soluble NOX2-derived peptide and 8-iso-prostaglandin F2a and a significant decrease in nitric oxide bioavailability, vitamin E levels, and flow-mediated dilatation); Jessica L. Fetterman, Rachel J. Keith, Joseph N. Palmisano, Kathleen L. McGlasson, Robert M. Weisbrod, Sana Majid, Reena Bastin, Mary Margaret Stathos, Andrew C. Stokes, Rose Marie Robertson, Aruni Bhatnagar & Naomi M Hamburg, *Alterations in Vascular Function Associated With the Use of Combustible and Electronic Cigarettes*, 9 J. AM. HEART ASS'N 1, 1 (2020) (finding measures of arterial stiffness including carotid-femoral pulse wave velocity, augmentation index, carotid-radial pulse wave velocity, and central blood pressures were abnormal amongst combustible and e-cigarette users and endothelial cells from combustible cigarette smokers and sole e-cigarette users produced less nitric oxide in response to A23187 stimulation compared with nonsmokers, suggestive of impaired endothelial nitric oxide synthase signaling); Cristina Nocella, Giuseppe Biondi-Zoccai, Sebastiano Sciarretta, Mariangela Peruzzi, Francesca Pagano, Lorenzo Loffredo, Pasquale Pignatelli, Chris Bullen, Giacomo Frati & Roberto Carnevale, *Impact of Tobacco Versus Electronic Cigarette Smoking on Platelet Function*, 122 AM. J. CARDIOLOGY 1477, 1477 (2018) (finding that within five minutes of using either a conventional cigarette or e-cigarette, changes in the levels of sCD40L, sPselectin, and platelet aggregation were detectable in both smokers and nonsmokers); Thomas Münzel, Omar Hahad, Marin Kuntic, John F. Keaney, John E Deanfield & Andreas Daiber, *Effects of Tobacco Cigarettes, E-Cigarettes, and Waterpipe Smoking on Endothelial Function and Clinical Outcomes*, 41 EUROPEAN HEART J. 4057, 4057–70 (2020) (reviewing pre-clinical and clinical studies regarding the link between endothelial dysfunction and cardiovascular and pulmonary diseases and finding that e-cigarette use increases endothelial dysfunction). *But see* Andrew C. Stokes, Wubin Xie, Anna E. Wilson, Hanqi Yang, Olusola A. Orimoloye, Alyssa F. Harlow, Jessica L. Fetterman, Andrew P. DeFilippis, Emelia J. Benjamin, Rose Marie Robertson, Aruni Bhatnagar, Naomi M. Hamburg & Michael J. Blaha, *Association of Cigarette and Electronic Cigarette Use Patterns With Levels of Inflammatory and Oxidative Stress Biomarkers Among US Adults: Population Assessment of Tobacco and Health Study*, 143 CIRCULATION 869, 869–71 (2021) (finding no difference in inflammatory and oxidative stress biomarkers between exclusive e-cigarette users and nonusers (no cigarettes or vaping) amongst participants in the PATH study).

[72] Patrice Marques, Laura Piqueras & Maria-Jesus Sanz, *An Updated Overview of E-Cigarette Impact on Human Health*, 22 RESPIRATORY RSCH. 1, 11 (2021).

[73] Cornelius et al., *supra* note 38, at 397, 399.

[74] David T. Levy, Jamie Tam, Luz María Sanchez-Romero, Yameng Li, Zhe Yuan, Jihyoun Jeon & Rafael Meza, *Public Health Implications of Vaping in the USA: The Smoking and Vaping Simulation Model*, 19 POPULATION HEALTH METRICS 1, 13 (2021).

exist on a continuum of risk, with ENDS products lower on the risk spectrum than combustible products.[75]

Public health researchers and FDA have placed a heavy focus on harms related to youth uptake of ENDS products.[76] Indeed, ENDS product use in tobacco-naïve individuals, particularly adolescents, is associated with the transition to combustible cigarette use and may engender nicotine dependence.[77] Nicotine, while not a direct carcinogen itself,[78] does exert pernicious and deleterious effects on the developing brain. Specifically, it has been shown in a combination of clinical and animal model studies to result in cognitive and behavioral impairments and more severe addiction (potentially including other substances) later in life.[79] While the TCA does list the importance of limiting youth uptake and use of all tobacco products, it also explicitly states that cessation by current users is a purpose of the Act.[80] This acknowledges that harm reduction (within the context of the Act continuing to allow combustible products) is a central tenet of the TCA. While regulating advertisements, point-of-sales restrictions, and some marketing approval/denial actions (especially regarding flavored ENDS products) may have benefits for limiting youth uptake, if they are a singular focus of ENDS product regulation, then FDA will leave the current millions of adult smokers behind.[81]

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[75] Letter from Clifford E. Douglas, Dir., Univ. of Mich. Tobacco Rsch. Network, to Robert Califf, Comm'r, U.S. Food & Drug Admin. (Mar. 8, 2022) (on file with authors); s*ee also* Cummings et al., *supra* note 38, at 7–8.

[76] NAT'L ACADS. OF SCIS., ENG'G & MED., PUBLIC HEALTH CONSEQUENCES OF E-CIGARETTES 493–532 (2018), https://www.nap.edu/catalog/24952/public-health-consequences-of-e-cigarettes.

[77] Samir Soneji, Jessica L. Barrington-Trimis, Thomas A. Wills, Adam M. Leventhal, Jennifer B. Unger, Laura A. Gibson, JaeWon Yang, Brian A. Primack, Judy A. Andrews, Richard A. Miech, Tory R. Spindle, Danielle M. Dick, Thomas Eissenberg, Robert C. Hornik, Rui Dang & James D. Sargent, *Association Between Initial Use of E-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-Analysis*, 171 JAMA PEDIATRICS 788, 790–96 (2017). However, note that alternative regulatory steps, such as regulating the nicotine levels in ENDS products in conjunction with lowering nicotine levels in combustible cigarettes over time, would theoretically make this transition less likely as it would result in a step down in nicotine.

[78] Robert P. Murray, John E. Connett & Lisa M. Zapawa, *Does Nicotine Replacement Therapy Cause Cancer? Evidence from the Lung Health Study*, 11 NICOTINE & TOBACCO RSCH. 1076, 1076 (2009).

[79] Hamed Salmanzadeh, S. Mohammad Ahmadi-Soleimani, Narges Pachenari, Maryam Azadi, Robert F. Halliwell, Tiziana Rubino & Hossein Azizi, *Adolescent Drug Exposure: A Review of Evidence for the Development of Persistent Changes in Brain Function*, 156 BRAIN RSCH. BULL. 105, 105 (2020). Currently, there are other controls in place to limit youth access to ENDS products, including increasing the legal age requirement to twenty-one, requiring scanning ID's at the point of sale, and limiting marketing strategies. FDA does tangentially regulate the latter by reviewing marketing plans, with particular focus on appeal to youth. FDA also requires PMTAs to show how appealing a product would be for both non-users (i.e., youth), as well as for current users. *See infra* Section IV.C for further discussion on how FDA analyzes marketing limitations during its review of PMTAs to determine if an ENDS product is APPH.

[80] TCA § 3(9).

[81] See generally *supra* note 41 for discussion of the limited success of medical therapy in achieving cessation among active smokers.

III. LEGAL HISTORY OF ENDS PRODUCT REGULATION

A. Statutory Authority

The TCA contained a glaring hole from the moment it was signed into law in 2009 because it did not include explicit authority for FDA to regulate ENDS products, which were already widely available for commercial sale.[82] Rather, the Act explicitly mentioned more traditional tobacco products such as cigarettes, cigars, pipe tobacco, roll-your-own tobacco, and smokeless tobacco. However, the Act did allow for unenumerated products to fall within FDA's regulatory scope as "any other tobacco products that the Secretary by regulation deems to be subject to this chapter."[83] Thus, it required a notice-and-comment rulemaking process for the FDA to claim regulatory authority. In its May 2016 Rule ("Deeming Rule"), FDA deemed ENDS products to fall within the statutory definition of "tobacco products" and thus under its regulatory control.[84] This decision was contested by ENDS product makers but ultimately upheld in both the U.S. District Court for the District of Columbia (July 21, 2017)[85] and the D.C. Circuit Court of Appeals (December 12, 2019).[86] In sum, it took almost eleven years to finally settle the question of whether FDA even had the legal authority to regulate ENDS products.

Meanwhile, FDA promulgated two public-facing documents related to ENDS product PMTA applications. One is the Final Rule on Premarket Tobacco Product Applications and Recordkeeping Requirements[87] ("PMTA Final Rule"), which underwent notice and comment rulemaking per the Administrative Procedure Act (APA).[88] This regulation is geared toward tobacco products, in general, rather than ENDS products, specifically. The second is the Guidance for Industry on Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems[89] ("ENDS PMTA Guidance"), which is specific for ENDS products. The Guidance is explicit that it does not "establish any rights for any person and is not binding on FDA or the public."[90]

The content of the ENDS PMTA Guidance document will be discussed in detail in Part IV of this Article. To summarize in administrative law parlance, the ENDS PMTA Guidance does not create binding norms that act prospectively, and it allows the

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[82] *See supra* notes 61–62 and accompanying text.

[83] TCA § 901(b) (codified at 21 U.S.C. § 387a(b)).

[84] Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products, 81 Fed. Reg. 28,974, 28,976 (May 10, 2016) (codified at 21 C.F.R. Part 1100) ("Deeming Rule").

[85] Nicopure Labs, LLC v. Food & Drug Admin., 266 F. Supp. 3d 360, 380 (D.D.C. 2017).

[86] Nicopure Labs, LLC v. Food & Drug Admin., 944 F.3d 267, 272 (D.C. Cir. 2019).

[87] Premarket Tobacco Product Applications and Recordkeeping Requirements, 86 Fed. Reg. 55,300 (Oct. 5, 2021) (codified at 21 C.F.R. §§ 1100, 1107, 1114).

[88] 5 U.S.C. § 553.

[89] U.S. FOOD & DRUG ADMIN., PREMARKET TOBACCO PRODUCT APPLICATIONS FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS (REVISED): GUIDANCE FOR INDUSTRY (Mar. 2023) [hereinafter ENDS PMTA GUIDANCE], https://www.fda.gov/media/127853/download.

[90] *Id.* at 1. Per administrative law principles, the ENDS PMTA Guidance does not carry the force of law. Chrysler Corp. v. Brown, 441 U.S. 281, 301–02, 302 n.31 (1979).

agency to genuinely exercise discretion when deciding whether to authorize or deny future regulatory submissions.[91] In fact, CTP's discretion in rejecting several PMTA applications is discussed in further detail in Sections IV.A.1.iii. and IV.B.3, *infra*. Thus, it is not a legislative rule that carries the weight of law. Moreover, it does not discuss any thresholds for ENDS product authorization that could serve as product standards.

B. Challenges with Timeliness

Concomitant to the rulemaking (Deeming Rule) and litigation supporting its authority to regulate ENDS products, FDA was also embroiled in litigation regarding the timeline for doing so. In August of 2017, it issued a Guidance for Industry[92] that reiterated the TCA's requirement for ENDS makers to file a PMTA but allowed existing products as well as new products to remain on the market through the exercise of enforcement discretion.[93] This August 2017 Guidance set the deadline for PMTA submissions as "2021 or 2022."[94] Alarmed by this timeline and the enforcement discretion allowing ENDS products, including flavored products, to remain on the market pending determinations on their PMTA, several medical societies and public health groups, including the American Academy of Pediatrics, the American Cancer Society, Cancer Action Network, and the American Heart Association, sought to vacate the Guidance as a violation of the TCA's requirement for premarket review prior to marketing or distribution to consumers.[95] On May 15, 2019, the U.S. District Court for the Southern District of Maryland sided with the Plaintiffs, ruling that the August 2017 Guidance violated the APA because, despite the fact it was called a "Guidance" by FDA, it was actually a legislative rule that required notice-and-comment rulemaking prior to enforcement.[96] Additionally, the court was concerned by

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[91] *See generally* Ronald M. Levin, *Rulemaking and the Guidance Exemption*, 70 ADMIN. L. REV. 263, 291–93 (2018) (discussing the "binding norms" test, including *Pacific Gas & Electric Co. v. Fed. Power Comm'n*, 506 F.2d 33 (D.C. Cir. 1974). *See also* Nat'l Mining Ass'n v. McCarthy, 758 F.3d 243, 253 (D.C. Cir. 2014); American Bus Ass'n v. United States, 627 F.2d 525 (D.C. Cir. 1980)).

[92] Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule: Guidance for Industry (Revised), 82 Fed. Reg. 37,459 (Aug. 10, 2017). Note that the Guidance document itself has been withdrawn and revised and the August 2017 iteration is no longer available publicly. Its contents are quoted in this Article as cited by the reviewing court (U.S. District Court for the District of MD) in *Am. Acad. of Pediatrics v. U.S. Food & Drug Admin.*, 379 F. Supp. 3d 461, 497 (D. Md. 2019).

[93] Am. Acad. of Pediatrics v. U.S. Food & Drug Admin., 379 F. Supp. 3d 461, 468 (D. Md. 2019). *See also* U.S. FOOD & DRUG ADMIN., ENFORCEMENT PRIORITIES FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS (ENDS) AND OTHER DEEMED PRODUCTS ON THE MARKET WITHOUT PREMARKET AUTHORIZATION (REVISED)—GUIDANCE FOR INDUSTRY (Apr. 2020), https://www.fda.gov/media/133880/download [hereinafter FDA, ENFORCEMENT PRIORITIES].

[94] *Am. Acad. of Pediatrics*, 379 F. Supp at 468.

[95] *Id.* at 468–69.

[96] *Id.* at 470. The court determined the August 2017 Guidance was actually a legislative rule because it effectively amended a prior legislative rule (to wit, the TCA) because it "include[d] commands, requirements, and order: It tells manufacturers when they must submit their applications, reports, and requests for new tobacco products. More fundamentally, these requirements cannot be reconciled with the Tobacco Control Act, as they 'run[ ] 180 degrees counter to the plain meaning of the [statute],' which set much more stringent deadlines." *Id. Accord* Mallinckrodt Inc. v. U.S. Food & Drug Admin., No. DKC-14-3607, 2015 WL 13091366, at *11–12 (D. Md. July 29, 2015) ("A rule is legislative if any one of the following four questions is answered in the affirmative: (1) whether in the absence of the rule there would not be an adequate legislative basis for . . . agency action to confer benefits or ensure the performance of duties, (2) whether the agency has published the rule in the Code of Federal Regulations, (3) whether the

the arbitrary and shifting nature of the deadlines set in the Guidance document,[97] and in a subsequent remedial order[98] set the deadline of September 9, 2020 as the date by which a PMTA must be submitted for a new tobacco product and a twelve-month limit on CTP's enforcement discretion to all those products to remain on the market pending its review (thus permitting new tobacco products covered by a submitted PMTA to remain on the market until September 9, 2021).

Unfortunately, by September 9, 2021 FDA still had not completed review of many of the 6.7 million PMTAs it had already received.[99] At that time, FDA had no statutorily imposed reporting requirements,[100] so the public was required to wait on *sua sponte* updates from FDA on its progress on working through the back log of submitted PMTAs. On March 16, 2022, outgoing CTP director Mitch Zeller reported to the Society for Research on Nicotine and Tobacco that 99% of PMTAs received—across all product classes—had been completed (with either an authorization, Marketing Denial Order, Refusal to Accept, or Refusal to File).[101] CTP did not reach a decision on JUUL (one of the market leader in ENDS product sales since 2016 with approximately 35% market share[102]) until June 23, 2022. This marketing denial order as well as its subsequent stay and the litigation between JUUL and FDA is discussed in Section IV.A.1.c, *infra*.

C. Problems Arise Due to a Lack of Transparency

As ENDS products began rising in popularity, the diversity of products and number of manufacturers also began to rise.[103] This led to a deep pool of brand new products that potentially had never been tested for safety but were nevertheless available for purchase. This unregulated space led to several unfortunate health outcomes. For example, in early 2019 there was a proliferation of acute lung injuries, most notably in previously healthy young adults, characterized by inflammatory and fibrotic damage to the lung parenchyma. It was discovered that the use of e-cigarettes or vape

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agency has explicitly invoked its general legislative authority, or (4) whether the rule effectively amends a prior legislative rule." (quoting Am. Mining Cong. v. Mine Safety & Health Admin., 995 F.2d 1106, 1112 (D.C. Cir. 1993))). *See also Nat'l Mining Ass'n v. Jackson*, 768 F. Supp.2d 34, 48 (D.D.C. 2011) (observing that, under these circumstances, "notice and comment are required") (quoting U.S. Telecom Ass'n v. FCC, 400 F.3d 29, 35 (D.C. Cir. 2005)).

[97] *Am. Acad. of Pediatrics*, 379 F. Supp. at 497 ("Certainly, its requirements are *more* favorable to manufacturers than the Tobacco Control Act, essentially lifting statutory prohibitions for five or more years and imposing obligations across a longer timeframe.") (emphasis in original).

[98] Am. Acad. of Pediatrics v. U.S. Food & Drug Admin., No. 18-00883 (D. Md. Apr. 22, 2020).

[99] Alex Norcia, *FDA Fails to Meet Deadline to Decide on PMTA Applications for Vapes*, FILTER (Sept. 9, 2021), https://filtermag.org/fda-deadline-fail-vapes/.

[100] Congress subsequently imposed reporting requirements for CTP in the Consolidated Appropriations Act of 2022, Pub. L. 117-103136 Stat. 49 § 112 (codified at 21 U.S.C. § 387v).

[101] Mitchell Zeller, Ctr. for Tobacco Products, U.S. Food & Drug Admin., *FDA Special Session at the 2022 Society for Research on Nicotine and Tobacco*, YOUTUBE at 12:10 (Mar. 16, 2022), https://www.youtube.com/watch?v=NVvYl-luA4M.

[102] Richard Craver, *Market Share Gap Keeps Shrinking Between JUUL and Vuse*, WINSTON-SALEM J. (Apr. 7, 2022), https://journalnow.com/business/local/market-share-gap-keeps-shrinking-between-juul-and-vuse/article_89f3c1f4-b613-11ec-b882-4325fc45c39b.html.

[103] 2016 SURGEON GENERAL REPORT, *supra* note 65, Figure 1.1, Diversity of e-cigarette products; *Vaping Devices (Electronic Cigarettes) DrugFacts*, NAT'L INST. ON DRUG ABUSE: NAT'L INSTS. OF HEALTH (Jan. 8, 2020), https://nida.nih.gov/publications/drugfacts/vaping-devices-electronic-cigarettes.

pens was a significant risk factor, leading to the moniker "e-cigarette, or vaping, product-associated lung injury" or "EVALI."[104] The majority of patients diagnosed with EVALI used products containing tetrahydrocannabinol, but 14% of patients with EVALI reported exclusive use of nicotine-containing products.[105] More specifically, vitamin E acetate, a semi-synthetic esterified version of vitamin E that was used as a carrier oil for tetrahydrocannabinol-containing vape cartridges, was found in bronchoalveolar-lavage samples from 94% of patients tested and in none of the samples from the healthy comparator group.[106] This crisis illustrated the direct consumer harm and broader public health effects from a dysfunctional regulatory framework that was unable to identify and address a core function of a product's regulation: protection against product adulteration.[107]

There has also been controversy about the nicotine concentration and dosing delivered by ENDS products. Nicotine, in and of itself, does not cause cancer. Rather, it is the neurologically active substance that leads to addiction (and thus subsequent long-term exposure to the disease-causing toxicants).[108] There are, however, potential downstream consequences and medical risks of exposing users to higher amounts of nicotine than commonly found in cigarettes: doing so could increase combustible use among either dual-users or serve as a gateway for never smokers. Moreover, given the paucity of long-term use data due to the relative recency of the emergence of ENDS products, some long-term morbidity and mortality independent of combustible use may subsequently come to light. Completely eliminating nicotine from ENDS products is a risky proposition, however, as it may have the unintended consequence of consumers switching back to combustible products. Indeed, one of the primary treatment strategies for tobacco use disorder is to use nicotine in other non-combustible forms as a nicotine replacement therapy (e.g., with gum, patches, or lozenges), leading many to question whether nicotine delivery via an ENDS product could serve the same purpose.[109] In fact, there is a growing body of clinical data from academic researchers that ENDS products are more effective than FDA-approved

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[104] Emily Kiernan, Eleanor S. Click, Paul Melstrom, Mary E. Evans, Mark R. Layer, David N. Weissman, Sarah Reagan-Steiner, Jennifer L. Wiltz, Susan Hocevar, Alyson B. Goodman & Evelyn Twentyman, *A Brief Overview of the National Outbreak of E-Cigarette, or Vaping, Product Use-Associated Lung Injury and the Primary Causes*, 159 CHEST J. 426, 426–31 (2021).

[105] Vikram P. Krishnasamy, Benjamin D. Hallowell, Jean Y. Ko, Amy Board, Kathleen P. Hartnett, Phillip P. Salvatore, Melissa Danielson, Aaron Kite-Powell, Evelyn Twentyman, Lindsay Kim, Alissa Cyrus, Megan Wallace, Paul Melstrom, Brittani Haag, Brian A. King, Peter Briss, Christopher M. Jones, Lori A. Pollack & Sascha Ellington, *Update: Characteristics of a Nationwide Outbreak of E-Cigarette, or Vaping, Product Use-Associated Lung Injury—United States, August 2019–January 2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 90, 90 (2020).

[106] Benjamin C. Blount et al., *Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI*, 382 NEW ENG. J. MED. 697, 697 (2020).

[107] The statutory definition of an "adulterated tobacco product" includes a tobacco product with any "added deleterious substance that may render the product injurious to health." Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 387b(1).

[108] *See generally* OFF. OF THE SURGEON GEN., PUB. HEALTH SERV., U.S. DEP'T OF HEALTH & HUM. SERVS., THE HEALTH CONSEQUENCES OF SMOKING: NICOTINE ADDICTION—A REPORT OF THE SURGEON GENERAL (1988), https://digirepo.nlm.nih.gov/ext/document/101584932X423/PDF/101584932X423.pdf.

[109] Brenna VanFrank & Letitia Presley-Cantrell, *A Comprehensive Approach to Increase Adult Tobacco Cessation*, 325 JAMA 232, 232 (2021).

nicotine replacement therapies, such as patches, gum, or lozenges, at promoting smoking cessation at six months.[110]

In light of the potential for ENDS products to serve as a consumer-directed harm reduction product for tobacco use disorder, another controversy arose regarding whether ENDS products could be regulated as a drug, device, or combination product, all of which are excluded from CTP regulation per the TCA. In January 2017, FDA issued a final rule (following notice and comment rulemaking procedure) that differentiated between a modified risk tobacco product (MRTP) (subject to CTP regulation) and a medical product (subject to Center for Drug Evaluation and Research, or CDER, regulation).[111] The distinguishing feature was that any product "intended for disease mitigation or prevention" would be regulated as a drug, device, or combination product and subject to demonstrating both safety and effectiveness in order to obtain approval as a medical product. MRTPs, on the other hand, would just have to "present relatively less risk of disease or be less harmful . . . but do not affirmatively act to mitigate, prevent, or otherwise treat disease" in order to obtain marketing authorization from CTP.[112] This overlapping definition led to even more confusion, especially as the description of an MRTP seemed to explicitly acknowledge that tobacco products (potentially including ENDS products) would be authorized with less of an evidentiary burden than what was required for CDER approval.

As the statutory definition of a "modified risk tobacco product" includes any tobacco product that is "use[d] to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products,"[113] the MRTP authorization pathway seemed like an opportune pathway through which to regulate ENDS products. However, FDA determined in its Deeming Rule that it would not accept MRTPs for the first wave of ENDS product review and would require the more detailed PMTA.[114] This approach starkly contrasts that of the United Kingdom's National Health Service (NHS), which as early as 2015 was publicizing that e-cigarettes were 95% less

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[110] Jamie Hartmann-Boyce, Nicola Lindsona, Ailsa R. Butler, Hayden McRobbie, Chris Bullen, Rachna Begh, Annika Theodoulou, Caitlin Notley, Nancy A. Rigotti, Tari Turner, Thomas R. Fanshawe & Peter Hajek, *Electronic Cigarettes for Smoking Cessation*, COCHRANE DATABASE SYSTEMATIC REVS. No. 11, at 1 (2022).

[111] FDA promulgated a rule clarifying that a product will be regulated as a drug, device, or combination product "(1) If the product is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease; or (2) if the product is intended to affect the structure or any function of the body in any way that is different from effects related to nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000." Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. 2,193, 2,194 (Jan. 9, 2017).

[112] *Id.* at 2,199. *See also* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 387k. For information and guidance related to FDA's implementation of the statute, see also *Modified Risk Tobacco Products*, U.S. FOOD & DRUG ADMIN. (Mar. 16, 2023), https://www.fda.gov/tobacco-products/advertising-and-promotion/modified-risk-tobacco-products; *Section 911 of the Federal Food, Drug, and Cosmetic Act—Modified Risk Tobacco Products*, U.S. FOOD & DRUG ADMIN. (Jan. 7, 2018), https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/section-911-federal-food-drug-and-cosmetic-act-modified-risk-tobacco-products.

[113] 21 U.S.C. § 387k(b)(1).

[114] Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products, 81 Fed. Reg. 28,974, 28,990 (May 10, 2016) (codified at 21 C.F.R. Part 1100) ("Deeming Rule").

dangerous than cigarettes.[115] Moreover, NHS actively encourages people to try to use ENDS products as a form of consumer-directed therapy to quit smoking.[116] FDA's public education efforts have been much more ambiguous, stating "noncombustible tobacco products may be less harmful than combustible cigarettes. However, there is not yet enough evidence to support claims that e-cigarettes and other ENDS are effective tools for quitting smoking."[117] Perhaps as a consequence of these mixed signals, as of 2019, only 17.4% of active smokers in the United States perceived ENDS products as less harmful than cigarettes, a prevalence that decreased since 2014.[118] Moreover, approximately 60% of the 2,058 physicians surveyed in 2018 and 2019 considered all forms of tobacco products to be equally harmful.[119]

These controversies further underscore the need for clear product standards, particularly as ENDS products will be regulated through the PMTA (and eventually the substantial equivalence) pathways available through CTP. They also raise the question whether the presence of nicotine should be the primary focus of regulation (as opposed to tobacco products, more generally) and have led to models of nicotine exposure-based regulation (e.g., "nicotine flux" as defined by the nicotine emitted per puff per second).[120] Given the lack of transparency regarding how to meet the APPH standard, academics and public health leaders have proposed alternative regulatory mechanisms that focus on harm reduction as the guiding principle to define "Appropriate for the Protection of the Public Health." One such proposal emphasizes how ENDS products with varying levels of risk (or harm reduction capabilities) should be processed by FDA.[121]

This Article argues that the best and most useful public health tool would be for FDA to issue clear and (when feasible) objective product standards, which would allow for users, public health officials, and ENDS product makers to have a clear understanding of what products will meet the APPH standard, targeting product development programs around a clear regulatory standard and ultimately improving the public health. The following sections discuss these potential product standards in detail, relying on the publicly available scientific literature. As the tobacco industry

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[115] Press Release, Public Health England, E-Cigarettes Around 95% Less Harmful Than Tobacco Estimates Landmark Review (Aug. 19, 2022), https://www.gov.uk/government/news/e-cigarettes-around-95-less-harmful-than-tobacco-estimates-landmark-review [hereinafter Press Release, Public Health England].

[116] *Vaping to Quit Smoking*, NAT'L HEALTH SERV., https://www.nhs.uk/better-health/quit-smoking/vaping-to-quit-smoking/.

[117] *E-Cigarettes, Vapes, and Other Electronic Nicotine Delivery Systems (ENDS)*, U.S. FOOD & DRUG ADMIN. (June 29, 2022), https://www.fda.gov/tobacco-products/products-ingredients-components/e-cigarettes-vapes-and-other-electronic-nicotine-delivery-systems-ends.

[118] Sooyong Kim, Saul Shiffman & Mark A. Sembower, *US Adult Smokers' Perceived Relative Risk on ENDS and its Effects on Their Transitions Between Cigarettes and ENDS*, 22 BMC PUB. HEALTH, Sept. 19, 2022.

[119] Cristine D. Delnevo, Michelle Jeong, Arjun Teotia, Michelle M. Bover Manderski, Binu Singh, Mary Hrywna, Olivia A. Wackowski & Michael B. Steinberg, *Communication Between US Physicians and Patients Regarding Electronic Cigarette Use*, 5 JAMA NETWORK OPEN, Apr. 15, 2022, at 1.

[120] *See, e.g.*, Thomas Eissenberg & Alan Shihadeh, *Nicotine Flux: A Potentially Important Tool For Regulating Electronic Cigarettes*, 17 NICOTINE & TOBACCO RSCH. 165 (2015).

[121] Brian J. Miller, Andrew B. Meshnick & Boris D. Lushniak, *Electronic Nicotine Delivery Systems: The Need for Continued Regulatory Innovation*, 32 TOBACCO CONTROL 375 (Aug. 13, 2021), https://tobaccocontrol.bmj.com/content/early/2021/08/12/tobaccocontrol-2021-056622.full.

has historically mischaracterized or even manipulated the scientific literature,[122] this Article strives to base its recommendations on reliable scientific evidence, much of which was initially funded by CTP (in a joint venture with the NIH) through two rounds of funding of Tobacco Centers of Regulatory Science (TCORS). These fourteen TCORS grantees, located within academic research centers, received $273 million in funding between 2013 and 2018[123] and $151 million between 2018 and 2022.[124] CTP also spends approximately $25 million in personnel and operating costs related to its leadership, management, and oversight programs per year,[125] including policy development, which has resulted in the issuance of forty-three guidance documents,[126] five proposed rules, fifteen final rules, and seven notices of proposed rulemaking (NPRMs).[127] Despite these hundreds of millions of dollars in expenditures, CTP has yet to promulgate any product standards in any of these promulgated policy documents. After discussing the available scientific evidence, the following sections argue that sufficient data exist upon which clear and objective product standards can be set at this time.

IV. SCOPING THE BATTLEGROUNDS FOR ENDS PRODUCT STANDARDS

FDA has already laid a significant amount of the groundwork in establishing product standards by determining what technical aspects of ENDS products are important to regulate. The ENDS PMTA Guidance,[128] last updated in March 2023, outlines what categories of information are required within a PMTA for an ENDS product, but does not take the critical step of defining objective cutoffs or even clearly delineating product standards that FDA would consider meeting the APPH standard for authorization in areas where there should be a reasonable scientific consensus. In this section, the existing data in the publicly available literature is analyzed to discuss which aspects of ENDS products have been well settled, as opposed to those which remain controversial. Conceptually, many of the controversies with ENDS products can be bifurcated into technical aspects that are finite and easy to measure. Those aspects will be discussed *infra* in Section IV.A. Other controversies revolve around consumer use and overall public health impact, which require very different scientific approaches to study and are generally more difficult to answer with bright line, objective cutoffs. Those aspects will be discussed *infra* in Section IV.B.

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[122] Lisa A. Bero, *Tobacco Industry Manipulation of Research*, 120 PUB. HEALTH REPS. 200 (2005).

[123] *Tobacco Products: Tobacco Centers of Regulatory Science (TCORS)*, U.S. FOOD & DRUG ADMIN. (Jan. 5, 2018), https://web.archive.org/web/20180725113926/https:/www.fda.gov/TobaccoProducts/PublicHealthScienceResearch/Research/ucm369005.htm.

[124] *Tobacco Centers of Regulatory Science (TCORS)*, U.S. FOOD & DRUG ADMIN. (Feb. 11, 2021), https://www.fda.gov/tobacco-products/research/tobacco-centers-regulatory-science-tcors.

[125] U.S. FOOD & DRUG ADMIN., REPORT TO THE HOUSE AND SENATE COMMITTEES ON APPROPRIATIONS: TOBACCO PRODUCT USER FEES—REPORT IN RESPONSE TO THE CONSOLIDATED APPROPRIATIONS ACT, 2021 2 (Nov. 2, 2021), https://www.fda.gov/media/155617/download.

[126] *See Guidance*, U.S. FOOD & DRUG ADMIN. (Apr. 3, 2023), https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

[127] *See Rules and Regulations*, U.S. FOOD & DRUG ADMIN. (Mar. 8, 2023), https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/rules-and-regulations.

[128] ENDS PMTA GUIDANCE, *supra* note 89.

A. Engineering/Manufacturing Aspects of ENDS Products

There have been four "generations" of ENDS products to date.[129] All four, most generally, contain a battery-powered heating element/coil that vaporizes the nicotine-containing liquid ("e-liquid") adjacent to the coil's surface. As the user inhales, the vapor is drawn away from the coil and condenses into an aerosolized mist. The differences in design between the four generations is beyond the scope of this paper, especially considering that the technical aspects of ENDS product regulation, as discussed in this section, is applicable to any ENDS product regardless of its generation.

1. E-Liquid/Nicotine Elements

i. Nicotine Content or Exposure

Nicotine is far from benign: overdose can be fatal. There is some controversy over what the lethal dose of nicotine in humans is.[130] Standard material safety datasheets, databases, and toxicology textbooks use the cutoff of a 60 mg dose (which is roughly equivalent to smoking five cigarettes simultaneously). Assuming first-order pharmacokinetics and 20% bioavailability, ingesting 60 mg of nicotine would equate to a plasma concentration of about 0.18 mg/L.[131] This cutoff appears to be very conservative, as post-mortem analyses of fatal nicotine intoxications have shown the lowest fatal whole blood concentration of 1.0 mg/L (which would equate to plasma concentrations of 4 mg/L).[132] This would suggest that the minimum fatal nicotine dose is closer to 500 mg, or about 8.3 times higher than the commonly referenced 60 mg dose. Indeed, one case report documents a person surviving after intentionally ingesting 4 grams (4000 mg) of pure nicotine during a suicide attempt.[133] Further, as discussed above, nicotine does not, in and of itself, cause cancer.[134]

The nicotine that is delivered systemically to an ENDS product user is based on several factors beyond the amount or concentration in the e-liquid.[135] The pH of the e-liquid can have an impact on how much nicotine is absorbable in the oral cavity and upper respiratory tract of users, with more unprotonated nicotine at high pHs, leading

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[129] Alison Breland, Eric Soule, Alexa Lopez, Carolina Ramôa, Ahmad El-Hellani & Thomas Eissenberg, *Electronic Cigarettes: What Are They and What Do They Do?*, 1394 ANNALS N.Y. ACAD. SCI. 5, 5 (2017).

[130] Bernd Mayer, *How Much Nicotine Kills a Human? Tracing Back the Generally Accepted Lethal Dose to Dubious Self-Experiments in the Nineteenth Century*, 88 ARCHIVES TOXICOLOGY 5, 5–7 (2014).

[131] Janne Hukkanen, Peyton Jacob III & Neal L. Benowitz, *Metabolism and Disposition Kinetics of Nicotine*, 57 PHARMACOLOGICAL REVS. 57, 84 fig. 3 (2005).

[132] John M. Corkery, Jennifer Button, Alessandro E. Vento & Fabrizio Schifano, *Two UK Suicides Using Nicotine Extracted From Tobacco Employing Instructions Available on the Internet*, 199 FORENSIC SCI. INT'L 9, 9–11 (2010); Biagio Solarino, Frank Rosenbaum, Benno Riesselmann, Claas T. Buschmann & Michael Tsokos, *Death Due to Ingestion of Nicotine-Containing Solution: Case Report and Review of the Literature*, 195 FORENSIC SCI. INT'L e19, e19–e22 (2010).

[133] Mayer, *supra* note 130, at 5 (citing M. Schmidt & Hesse, *Nikotin-Vergiftung (Selbstmordversuch)*, 2 ARCHIVES TOXICOLOGY 15, 15–16 (1931).

[134] Murray et al., *supra* note 78, at 1076.

[135] *See generally* Natalie Voos, Maciej L. Goniewicz & Thomas Eissenberg, *What is the Nicotine Delivery Profile of Electronic Cigarettes*, 16 EXPERT OP. ON DRUG DELIVERY 1193 (2019).

to increased absorption.[136] Additionally, the amount of nicotine delivered is also a derivative of the power of the battery/coil, the ratio of PG/VG as the e-liquid solvent, as well as user behavior (e.g., puff duration).[137] There are several methods of measuring nicotine content (as well as content of other additives and toxicants, discussed *infra* in Section IV.A.1.iii), the most common of which is to use a machine that simulates puffing and can collect the aerosols generated onto a film that can then be analyzed for compound identity and quantification. A review of multiple studies using this system across different generations of ENDS products and different puffing conditions found that an ENDS product can produce far greater or far less aerosolized nicotine than an average cigarette (which is 1.76 to 2.20 mg per full cigarette).[138]

FDA requires testing and disclosing the nicotine concentration or strength[139] as well as warning labels that disclose the addictive properties and toxic properties of nicotine (e.g., "Avoid contact with skin and eyes. Do not drink. Keep out of reach of children and pets.").[140] While FDA has not explicitly listed any objective cutoffs for authorization, it has already authorized an ENDS product containing a 6% nicotine e-liquid (NJOY DAILY EXTRA Rich Tobacco 6%, authorized June 10, 2022).[141] FDA, however, did not disclose (nor has NJOY published) how the 6% concentration in this specific e-liquid translates to actual nicotine content in a user's plasma or serum. Thus, prior to issuing a bright line cutoff for nicotine content, FDA should establish a measurement standard for nicotine dosing akin to proof for alcohol or milligrams for small molecule drugs. As outlined in this section, there are enough reliable data regarding the harms of toxic levels of nicotine in and of itself for FDA, in collaboration with public health researchers and industry, to make these measurement standards.

ii. Additives

The most common solvent or humectant used in ENDS products is a combination of propylene glycol (PG) and/or vegetable glycerin (VG). Vaporizing glycerol produces the toxin acrolein (at least nine-fold less concentration than combustible cigarettes).[142] There are also concerns that both propylene glycol and glycerol can decompose at high temperatures to form the carcinogens formaldehyde and

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[136] Joseph G. Lisko, Hang Tran, Stephen B. Stanfill, Benjamin C. Blount & Clifford H. Watson, *Chemical Composition and Evaluation of Nicotine, Tobacco Alkaloids, pH, and Selected Flavors in E-Cigarette Cartridges and Refill Solutions*, 17 NICOTINE & TOBACCO RSCH. 1270, 1270 (2015); James F. Pankow, *A Consideration of the Role of Gas/Particle Partitioning in the Deposition of Nicotine and Other Tobacco Smoke Compounds in the Respiratory Tract*, 14 CHEM. RSCH. TOXICOLOGY 1465, 1465–81 (2001).

[137] Soha Talih, Zainab Balhas, Rola Salman, Rachel El-Hage, Nareg Karaoghlanian, Ahmad El-Hellani, Mohamad Baassiri, Ezzat Jaroudi, Thomas Eissenberg, Najat Saliba & Alan Shihadeh, *Transport Phenomena Governing Nicotine Emissions from Electronic Cigarettes: Model Formulation and Experimental Investigation*, 51 AEROSOL SCI. & TECHNOL. 1, 1–11 (2017).

[138] Voos et al., *supra* note 135, at 1196–97.

[139] The Child Nicotine Poisoning Prevention Act of 2015 (Pub. L. 114-116).

[140] ENDS PMTA GUIDANCE, *supra* note 89, at 16.

[141] U.S. Food & Drug Admin., Technical Project Lead (TPL) Review of PMTAs: PM0000630-PM0000631 (June 10, 2022), https://www.fda.gov/media/165234/download [hereinafter FDA, TPL Review].

[142] Maciej Lukasz Goniewicz, Jakub Knysak, Michal Gawron, Leon Kosmider, Andrzej Sobczak, Jolanta Kurek, Adam Prokopowicz, Magdalena Jablonska-Czapla, Czeslawa Rosik-Dulewska, Christopher Havel, Peyton Jacob III & Neal Benowitz, *Levels of Selected Carcinogens and Toxicants in Vapor from Electronic Cigarettes*, 23 TOBACCO CONTROL 133 (2014).

acetaldehyde, with aerosolized content dependent on battery output voltage (although formaldehyde is still thirteen-fold less than observed in combustible cigarettes).[143] A study found formaldehyde only at its high voltage setting (5.0V) but not at its low voltage setting (3.3V).[144] Other additives commonly include flavorants or sweeteners. The risks of flavors or sweeteners comes in two forms: toxicologic and behavioral (i.e., how they will be used by consumers). The marketing denial order for flavored ENDS products was based on its impact on user uptake, particularly among youth, rather than its toxicology profile. Thus, flavored-product standards will be discussed *infra* in Section III.B.3. For PMTAs, FDA requests information regarding the identity, concentrations, and stability information for each additive.[145] This information should include the established shelf life of the product and changes in pH and constituents (including Harmful or Potentially Harmful Constituents (HPHCs) and other toxic chemicals) over the lifespan of the product, such as the factors that determine the shelf life.

For the purposes of evaluating additives in ENDS products, especially while creating product standards, the chemical or toxicologic properties of the additives are more relevant in their aerosolized forms. As the components in the e-liquid are vaporized on the heating coil and converted into an aerosol, other chemical transformations can occur, leading to potential HPHC generation.[146] Testing the aerosols produced by an ENDS product is commonly done using the puffing machine and filter system described above, with chemical component analysis being completed via gas chromatography and mass spectrometry.[147] This technique is a non-targeted approach that is able to detect and identify thousands of potential compounds in the sample. It can also quantify those chemical components.

The toxicologic risk of flavors and other additives in ENDS products can therefore be elucidated by analyzing the chemicals in the aerosol. In its ENDS PMTA Guidance, FDA does request an analysis of aerosolized compounds.[148] It also requests that "a strong scientific justification for the potential daily exposure levels of users to an aerosol from an ENDS product should be included."[149] FDA additionally recommends that applicants "provide the scientific rationale for the selection of the daily exposure to any other tobacco products used as comparators."[150] Thus, rather than making quantifiable cutoffs for any flavor or other additive, ENDS product standards should focus on general toxicology (to wit, the identity and quantity of HPHCs) as discussed in further detail in the next section. By comparing total HPHCs in ENDS products to

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[143] Leon Kosmider, Andrzej Sobczak, Maciej Fik, Jakub Knysak, Marzena Zaciera, Jolanta Kurek & Maciej Lukasz Goniewicz, *Carbonyl Compounds in Electronic Cigarette Vapors: Effects of Nicotine Solvent and Battery Output Voltage*, 16 NICOTINE & TOBACCO RSCH. 1319, 1319 (2014).

[144] R. Paul Jensen, Wentai Luo, James F. Pankow, Robert M Strongin & David H. Peyton, *Hidden Formaldehyde in E-Cigarette Aerosols*, 372 NEW ENG. J. MED. 392 (2015).

[145] ENDS PMTA GUIDANCE, *supra* note 89, at 28–30.

[146] *Vaping Devices (Electronic Cigarettes) DrugFacts*, *supra* note 103, at 1–2.

[147] Justyna Aszyk, Mateusz Kacper Woźniak, Paweł Kubica, Agata Kot-Wasik, Jacek Namieśnik & Andrzej Wasik, *Comprehensive Determination of Flavouring Additives and Nicotine in E-Cigarette Refill Solutions. Part II: Gas-Chromatography–Mass Spectrometry Analysis*, 1517 J. CHROMATOGRAPHY A 156 (2017).

[148] ENDS PMTA GUIDANCE, *supra* note 89, at 30–32.

[149] *Id.* at 40.

[150] *Id.*

those found in combustible products, FDA can ensure that its ENDS product standards will indeed result in a less harmful product that could be APPH.

iii. Toxicology

In its ENDS PMTA Guidance, FDA asked applicants to consider assessing the presence of thirty-three constituents in e-liquids and/or aerosols.[151] The ENDS PMTA Guidance stated that these thirty-three compounds "potentially could" cause health hazards depending on the level, absorption, or interaction with other constituents.[152] This list was drawn from its experience in testing combustible tobacco products, and indeed, many of the thirty-three compounds are only produced as a result of the chemical reaction of combustion (i.e., cannot possibly be produced by ENDS products).[153] FDA additionally stated that "[o]ther constituents, as appropriate for your particular product [may require analysis]. For example, you might want to consider whether you should test for flavorants that can be respiratory irritants such as benzaldehyde, vanillin, and cinnamaldehyde."[154]

A highly cited publication in toxicology research tested thirty-four ENDS products and fifty-seven e-liquids commercially available in Canada, U.K., Poland, France, and South Africa from 2015–2018. The researchers compared the aerosolized contents of the commercially available products to a lab-created reference sample and air blanks as a negative control. They measured five heavy metals, four tobacco-specific nitrosamines, three carbonyls, and three additional HPHCs (benzene, 1,3-butadiene, and benzo(a)pyrene), which included twelve of the aforementioned thirty-three identified by FDA in the ENDS PMTA Guidance, and found that the HPHCs were generally not detectable in the ENDS products with the notable exception of formaldehyde, which was comparable to its content in cigarettes in some devices, but significantly reduced in other devices such as cartridge-based systems.[155]

In-human toxicology studies have shown that ENDS products users have significantly less exhaled carbon monoxide (a known cardiovascular toxicant) as well as lower serum concentrations of 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (a known lung carcinogen), with a seven-fold decrease in third generation devices

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[151] *Id.* at 31–32 (Acetaldehyde, Acetyl propionyl (also known as 2,3-pentanedione), Acrolein, Acrylonitrile, Benzene, Benzyl acetate, Butyraldehyde, Cadmium, Chromium, Crotonaldehyde, Diacetyl, Diethylene glycol, Ethyl acetate, Ethyl acetoacetate, Ethylene glycol, Formaldehyde, Furfural, Glycerol, Glycidol, Isoamyl acetate, Isobutyl acetate, Lead, Menthol, Methyl acetate., N-butanol, Nickel, Nicotine (from any source, including total nicotine, unprotonated nicotine, and nicotine salts), NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), NNN (N-nitrosonornicotine), Propionic acid, Propylene glycol, Propylene oxide, and Toluene).

[152] *Id.* at 31.

[153] Karl A. Wagner, Jason W. Flora, Matt S. Melvin, Karen C. Avery, Regina M. Ballentine, Anthony P. Brown & Willie J. McKinney, *An Evaluation of Electronic Cigarette Formulations and Aerosols for Harmful and Potentially Harmful Constituents (HPHCs) Typically Derived from Combustion*, 95 REGULATORY TOXICOLOGY & PHARMACOLOGY 153, 158 (2018). *Compare* ENDS PMTA GUIDANCE, *supra* note 89, at 30–32, *with* U.S. FOOD & DRUG ADMIN., REPORTING HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN TOBACCO PRODUCTS AND TOBACCO SMOKE UNDER SECTION 904(A)(3) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT: DRAFT GUIDANCE 2–4 (Mar. 2012), https://www.fda.gov/media/83375/download.

[154] ENDS PMTA GUIDANCE, *supra* note 89, at 31–32.

[155] Maxim Belushkin, Donatien Tafin Djoko, Marco Esposito, Alexandra Korneliou, Cyril Jeannet, Massimo Lazzerini & Guy Jaccard, *Selected Harmful and Potentially Harmful Constituents Levels in Commercial E-Cigarettes*, 33 CHEM. RSCH. TOXICOLOGY, 657 (2019).

compared to combustible tobacco.[156] A small cross-sectional study found lower urine and salivary concentrations of tobacco-specific N-nitrosamines (TSNAs) and volatile organic compounds (VOCs) in those who exclusively used ENDS-products for at least six months.[157] However, at least four of the HPHCs from FDA's list that were not included in the aforementioned study were subsequently found to be elevated in ENDS product users compared to non-smokers: acrylonitrile, acrolein, crotonaldehyde, and propylene oxide.[158]

FDA intended to establish a revised list of HPHCs that include HPHCs found only in ENDS products.[159] Unfortunately, when FDA last proposed revisions to the HPHC list on August 4, 2019, FDA did not suggest a list of ENDS-specific HPHCs.[160] There is also a separate statutory requirement to submit HPHC listings (§ 904) in addition to the information required in a PMTA (§ 910). As discussed in detail below, the quantity of data required by FDA in its ENDS PMTA Guidance is significant. Thus, FDA should be required to publish a list of ENDS-specific HPHCs based on its intramural research findings (which the agency has not made public) as well as the toxicology data submitted by industry in PMTAs (also not made public due to concerns over trade secrets).

a. Evidentiary Requirement

In the ENDS PMTA Guidance, FDA requests the following forms of toxicology data to support a PMTA:

- Toxicology data from the literature (i.e., all relevant publications);
- Analysis of constituents, including HPHCs and other toxicants, under both intense and non-intense use conditions;
- In vitro toxicology studies (e.g., genotoxicity studies, cytotoxicity studies);
- Computational modeling of the toxicants in the product (to estimate the toxicity of the product); and
- In vivo toxicology studies (to address unique toxicology issues that cannot be addressed by alternative approaches).[161]

Studies in animal models are useful in toxicology insofar as they can more aggressively test the upper limits of tolerability in ways that would not be ethical in

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[156] Theodore L. Wagener, Evan L. Floyd, Irina Stepanov, Leslie M. Driskill, Summer G. Frank, Ellen Meier, Eleanor L. Leavens, Alayna P. Tackett, Neil Molina & Lurdes Queimado, *Have Combustible Cigarettes Met Their Match? The Nicotine Delivery Profiles and Harmful Constituent Exposures of Second-Generation and Third-Generation Electronic Cigarette Users*, 26 TOBACCO CONTROL 23, 23 (2017).

[157] Lion Shahab, Maciej L. Goniewicz, Benjamin C. Blount, Jamie Brown, Ann McNeill, K. Udeni Alwis, June Feng, Lanqing Wang & Robert West, *Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-Sectional Study*, 166 ANNALS INTERNAL MED. 390, 390 (2017).

[158] Mark L. Rubinstein, Kevin Delucchi, Neal L. Benowitz & Danielle E. Ramo, *Adolescent Exposure to Toxic Volatile Organic Chemicals From E-Cigarettes*, 141 PEDIATRICS 1 (2018).

[159] Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions; Request for Comments, 84 Fed. Reg. 38,032, 38,033 (Aug. 5, 2019).

[160] *Id.* at 38,034–35.

[161] ENDS PMTA GUIDANCE, *supra* note 89, at 37–38.

human studies. However, this aggressive experimental dosing can be a double-edged sword, as it makes it difficult to extrapolate to human use. Within these limitations, in vivo animal studies recently reviewed by Cao et al. demonstrate that exposure to aerosolized ENDS products can cause lung inflammation, cardiac defects, reproductive organ suppression, fetal developmental delay, neurotoxicity, and altered systemic proteomics in a wide variety of animal and exposure models.[162] However, these authors did not attempt to compare aerosolized ENDS product exposure to combustible exposure in these various animal models. One study did find significantly less structural lung damage, inflammatory protein production, and leaking of proteinaceous fluid into alveolar airspace, despite higher total particulate exposure in the e-cigarette group compared to the combustible exposure group.[163]

The ENDS PMTA Guidance goes on to request that applicants conduct studies on the specific product (unless already conducted and published by independent researchers). For any studies conducted prospectively, FDA recommends that applicants consider the following points:

- Studies should be based on the potential human exposure of the product. Exposures that mimic the highest consumer use scenario and one lower exposure level should be evaluated in the toxicology studies based on the results determined as described in section VI.H.1.a. Analysis of constituents and toxicant levels at the exposures tested should be included.
- If the consumer can change the voltage and/or temperature of the heating element, we recommend that you provide any available data on the subsequent changes in the aerosol ingredients. Please also include any toxicity information relevant to these changes.
- We recommend that you provide aerosolization properties of each of the ingredients (e.g., constituents, humectants, metals, flavors included), particle size of these ingredients in the product, and deposition of these particles through inhalation. We also recommend that you discuss how these properties could affect the product's toxicity profile.
- In vitro assays can be used to evaluate the genotoxic potential of the ENDS in comparison to other tobacco products. We suggest using the ICH S2(R1) guidance Organization for Economic Cooperation and Development protocols as a guide for genotoxicity assessment. We also recommend that you conduct these assays with multiple concentrations of your final product for validating your results. For appropriate hazard identification

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[162] Yuna Cao, Daming Wu, Ying Ma, Xinmo Ma, Shile Wang, Fuxian Li, Menghan Li & Ting Zhang, *Toxicity of Electronic Cigarettes: A General Review of the Origins, Health Hazards, and Toxicity Mechanisms*, 772 SCI. TOTAL ENV'T 1 (2021).

[163] Ahmad Husari, Alan Shihadeh, Soha Talih, Yasmine Hashem, Marwan El Sabban & Ghazi Zaatari, *Acute Exposure to Electronic and Combustible Cigarette Aerosols: Effects in an Animal Model and in Human Alveolar Cells*, 18 NICOTINE & TOBACCO RSCH. 9 (2016).

> comparison, you should include the comparator products (e.g., products in the same category) in your in vitro assay.[164]

Moreover, FDA expected that applicants would report the levels of HPHCs as appropriate for each product, so the reported HPHCs would differ among different product categories. It additionally recommended that manufacturers consult with CTP's Office of Science about what is appropriate in the context of a specific application.[165]

b. JUUL MDO and Appeal

On June 23, 2022, FDA issued a marketing denial order for all products manufactured by JUUL, stating that JUUL's application:

> [L]acked sufficient evidence regarding the toxicological profile of the products to demonstrate that marketing of the products would be appropriate for the protection of the public health. In particular, some of the company's study findings raised concerns due to insufficient and conflicting data—including regarding genotoxicity and potentially harmful chemicals leaching from the company's proprietary e-liquid pods—that have not been adequately addressed and precluded the FDA from completing a full toxicological risk assessment of the products named in the company's applications.[166]

JUUL appealed the adjudication the same day, seeking a stay on the grounds that FDA's decision was arbitrary and capricious. By the following day, the U.S. Court of Appeals for the D.C. Circuit put a stay on FDA's order based on, *inter alia*, JUUL's likelihood of winning the case against FDA on its merits.[167] Eleven days later, FDA self-imposed a stay on its own order, stating on its website and Twitter that "The agency has determined that there are scientific issues unique to the JUUL application that warrant additional review."[168]

More specifically, FDA's marketing denial order stated that JUUL's PMTA did not include testing for four HPHCs, two of which were potential "leachables" (i.e., a product of combining the e-liquid with the materials of the enclosure system under high heat conditions).[169] Unfortunately for the public, the identity of those four compounds has been redacted in the litigation materials.[170] Per JUUL's court filings, it submitted a PMTA that included over 110 scientific references and 125,000 pages

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[164] *Id.* at 39.

[165] *Id.* at 28.

[166] Press Release, U.S. Food & Drug Admin., FDA Denies Authorization to Market JUUL Products (June 23, 2022), https://www.fda.gov/news-events/press-announcements/fda-denies-authorization-market-juul-products [hereinafter FDA, JUUL Press Release].

[167] Petitioner Juul Labs, Inc.'s Corrected Redacted Emergency Motion for Stay Pending Review, Juul Labs, Inc. v. U.S. Food & Drug Admin., No. 22-1123 (D.C. Cir. June 28, 2022).

[168] FDA, JUUL Press Release, *supra* note 166; @FDATobacco, TWITTER (July 1, 2022, 10:05 AM), https://twitter.com/FDATobacco/status/1542872142647287810.

[169] Petitioner Juul Labs, Inc.'s Corrected Redacted Emergency Motion for Stay Pending Review, Juul Labs, Inc. v. U.S. Food & Drug Admin, No. 22-1123 at 10 (D.C. Cir. June 28, 2022).

[170] *Id.* at 16.

of data and analysis.[171] Additionally, they averred that FDA only communicated with them once regarding any data deficiencies in its PMTA, and the company responded to it promptly, making the June 2022 denial somewhat surprising.[172]

In terms of its toxicologic testing, JUUL conducted mass spectroscopy analysis to identify and quantify all possible HPHCs. Per their legal pleadings—the data are not currently publicly available—this showed a 98% or greater reduction in HPHCs compared to combustible cigarettes.[173] Additionally, JUUL completed a targeted screen as well, to assess for the specific toxicants of concern by FDA (see list of thirty-three HPHCs, *supra* note 151) using methods approved by EPA for specific-toxicant detection.[174] JUUL claimed that it submitted at least 6,000 pages of data and other scientific information regarding its toxicologic testing.[175] As of the writing of this paper, FDA has not re-issued its decision on JUUL's PMTA after withdrawing its initial MDO on July 1, 2022.

JUUL subsequently submitted requests under the Freedom of Information Act (FOIA) for the agency to release its internal documents supporting the rationale behind its original MDO.[176] After FDA withheld some of the requested documents, citing the "deliberative process privilege," JUUL sued on September 20, 2022, arguing that the privilege no longer applies after the agency issued the MDO in June insofar as the requested documents reflected final agency action or its rationale.[177] In contrast to this lack of transparency, FDA customarily submits a complete response letter to the manufacturer of a new drug[178] or biologic[179] if it chooses to reject their applications for marketing approval.[180] While these complete response letters are not automatically published by FDA, they are publicly available via FOIA requests.[181]

FDA's (initial) MDO for all JUUL products based on toxicology is perplexing, as toxicology offers an area where quantifiable, objective cutoffs can be established. Guiding principles for establishing product standards with objective, quantitative

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[171] *Id.* at 7, 39.

[172] *Id.* at 7, 9.

[173] *Id.* at 9.

[174] *Id.* at 39. *See generally PFAS Analytical Methods Development and Sampling Research*, U.S. ENV'T PROT. AGENCY, https://www.epa.gov/water-research/pfas-analytical-methods-development-and-sampling-research (last visited May 3, 2023).

[175] Petitioner Juul Labs, Inc.'s Corrected Redacted Emergency Motion for Stay Pending Review at 16, Juul Labs, Inc. v. U.S. Food & Drug Admin., No. 22-1123 at 2, 8, 43.

[176] Robert S. Claiborne, Jr., Bryan M. Haynes & Agustin E. Rodriguez, *Juul Labs, Inc. v. FDA: A FOIA Twist on the Challenge to FDA's Marketing Denial Order*, FOOD & DRUG L. INST., UPDATE MAG. (Summer 2023), https://www.fdli.org/2023/05/juul-labs-inc-v-fda-a-foia-twist-on-the-challenge-to-fdas-marketing-denial-order/.

[177] Jonathan Stempel, *Juul Sues FDA for Documents Said to Justify E-Cigarette Ban*, REUTERS (Sept. 20, 2022), https://www.reuters.com/legal/juul-sues-fda-documents-said-justify-e-cigarette-ban-2022-09-20/. *See generally* U.S. Fish & Wildlife Serv. v. Sierra Club, Inc., 141 S. Ct. 777, 785–86 (2021).

[178] 21 C.F.R. § 314.110 (2023).

[179] 21 C.F.R. § 601.3 (2023).

[180] *See also* Peter Lurie, Harinder S. Chahal, Daniel W. Sigelman, Sylvie Stacy, Joshua Sclar & Barbara Ddamulira, *Comparison of Content of FDA Letters Not Approving Applications for New Drugs and Associated Public Announcements from Sponsors: Cross Sectional Study*, BMJ, June 10, 2015.

[181] Peter Lurie et al., *Public Citizen Gripes FDA Too Slow in Making Drug Reviews Public*, INSIDE WASH.'S FDA WK., May 5, 2001, at 11.

cutoffs should focus on the available evidence, especially as it relates to combustible cigarettes. Although there have been some HPHCs discovered that are unique to ENDS products (e.g., acrylonitrile, crotonaldehyde, and propylene oxide), similar cutoffs could be established. Thus, it is essential that PMTA applicants perform a non-targeted analysis of their aerosolized product to positively identify and quantify any potential HPHC that may be unique to their products. As ENDS products are a tool for harm reduction, the toxicologic product standards should reflect that promise: no HPHC that is also found in combustible tobacco products should be found in higher quantities than in combustible cigarettes. Moreover, taken in total, there should be at least a pre-specified reduction in the total quantity of all cumulative HPHCs on a puff-by-puff comparison to cigarette combustion.

2. Engineering/Design Elements

i. Heating coil/voltage/wattage

There are relatively few publications in the literature regarding different heating coils and their impact on the performance or toxicology of ENDS products. One group constructed an atomizer system using a heating coil constructed from ferritic iron-chromium-aluminum alloy (called Kanthal A1) and measured the amount of metallic nanoparticles produced at different coil resistances, applied power levels, and duty cycles.[182] The study measured metallic nanoparticles created by heating the coil itself and did not measure all potential HPHCs discussed in the previous section. The authors found significant increases in metallic nanoparticle production as all three of their testing conditions increased.[183] However, neither their study design nor preexisting information in the published literature allowed them to conclude whether the metallic nanoparticles are toxic or threatening human health.[184] Interestingly, the authors did note that their lab-created heating coils showed a steep decrease in metallic nanoparticle production with repeated use, making the authors hypothesize that an oxidative reaction on the surface of the coil (e.g., aluminum into alumina) may be protecting the coil from degrading and emitting the metallic nanoparticles with further use.[185]

Heating the e-liquids to different temperatures has the potential of transforming some of the HPHCs into others (e.g., "leachables" discussed *supra*, note 169 and accompanying text).[186] In the absence of studies that correlate heating coil settings to toxicant exposure,[187] product standards can still be set by referencing the heating coil settings used in the numerous toxicology studies discussed *supra* in Section IV.A.1

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[182] Mark D. Wilson, Kaushal A. Prasad, Jong Sung Kim & Jae Hong Park, *Characteristics of Metallic Nanoparticles Emitted from Heated Kanthal E-Cigarette Coils*, 21 J. NANOPARTICLE RSCH. 1 (2019).

[183] *Id.* at 5, 7.

[184] *Id.* at 7–9.

[185] *Id.* at 9.

[186] *See, e.g.*, Nathalie Gonzalez-Jimenez, Naudia Gray, R. Steven Pappas, Mary Halstead, Erica Lewis, Liza Valentin-Blasini, Clifford Watson & Benjamin Blount, *Analysis of Toxic Metals in Aerosols from Devices Associated with Electronic Cigarette, or Vaping, Product Use Associated Lung Injury,* 9 TOXICS 240, 240 (2021).

[187] Sebastien Soulet & Roberto A. Sussman. *Critical Review of the Recent Literature on Organic Byproducts in E-Cigarette Aerosol Emissions*, 10 TOXICS 714 (2022).

and accompanying notes. In those studies, coils were frequently set at 70 Watts of applied power and up to a 1.0 ohms of resistance.[188]

ii. Product Dimensions

FDA has not issued any specifications regarding product dimensions, other than the requirement that applicants list them. However, based on the discussion *supra* in Sections IV.A.1.i and IV.A.2, the main safety concern stemming from product dimensions should be to limit the potential for nicotine toxicity or overdose. This Article recommends that either product dimensions (especially e-liquid quantity) or puff topography demonstrate that a potentially fatal dose cannot be reached. Puff topography is discussed further as a component of "user topography" *infra* in Section IV.B.

iii. Closure System

FDA requires that applicants include information on how the container closure system protects and preserves the product, such as from damage during transport, environmental contaminants, leaching, and migration of container closure system constituents into the products. The agency allows this information to be generated by the applicant, by the supplier of the material of construction or the component, or by a laboratory under contract to either the applicant or the manufacturer.

In addition to chemical/toxicologic concerns, FDA is interested in durability and other design features, requiring prior testing by the manufacturer. The ENDS PMTA Guidance calls for:

> [T]he explicit range of or the nominal values of the design features as well as the design tolerance, where appropriate; A quantitative description of the performance specifications; A description of product container closure system. The description should include information on how the container closure system protects and preserves the product, such as from damage during transport, environmental contaminants, leaching, and migration of container closure system constituents into the products (FDA expects that this documentation may be generated by the applicant, by the supplier of the material of construction or the component, or by a laboratory under contract to either the applicant or the manufacturer).[189]

These requirements also help identify potential adulterations to the product, such as altering the product to deliver illicit substances.[190]

3. Manufacturing

Controls for product consistency are important, as several studies have found wide discrepancies between the nicotine content found on the label and what was tested in

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[188] *Id. See also* Wilson et al., *supra* note 182, at 3.

[189] ENDS PMTA GUIDANCE, *supra* note 89, at 29.

[190] *See, e.g.*, Henningfield & Slade, *supra* note 60, at 56–57 (discussing Premier and Eclipse products, the former of which was pulled after a few months of consumer testing in St. Louis and Phoenix due, in part, to how easily the device was able to be repurposed as a crack cocaine delivery system).

the e-liquid. Some of these discrepancies were quite large (-42% to +52%).[191] Another study using samples from the United States, South Korea, and Poland found that approximately one-quarter of samples had greater than 20% difference (above or below) the labeled amount.[192] Even among samples labeled and marketed as having zero nicotine, 91% had detectable amounts of nicotine, including as high as 23.9 mg/ml.[193]

On March 10, 2023, FDA issued a proposed rule on the requirements for tobacco product manufacturing processes (TPMP).[194] The proposed rule applies to all categories of tobacco products (including ENDS products) and employs a quality system management approach, similar to how FDA regulates manufacturing quality standards in other product classes.[195] The stated goals of the TPMP rules are to "establish and maintain procedures for various aspects of the manufacturing, preproduction design validation, packing, and storage processes" in order to "ensure that tobacco products conform to established specifications and to help prevent the manufacture and distribution of contaminated or otherwise nonconforming products."[196] FDA specifically mentions ENDS products with nicotine concentrations that differ from the amount reported on the label as a nonconforming product under this proposed rule.[197] These TPMP standards would ensure product consistency and minimize contamination during the manufacturing process, but would not set authorization standards and thus serve a different function than the product standards we seek to describe in this Article.

B. Population-Level Aspects of ENDS Products

The overall impact of ENDS products on public health remains an outstanding question, largely because of the lack of long-term data on both morbidity and mortality. This paucity of data can be attributed to the relative novelty of ENDS products as a widely available commercial product and the delay between product use and disease onset (for most diseases caused by tobacco, risk from tobacco use is calculated in pack-years, or number of years of smoking one pack of cigarettes per day). However, as noted *supra* in Section IV.A.1.iii, there are HPHCs that exist in ENDS products at lower concentrations than in combustible products, and some HPHCs that are unique to ENDS products. How, if at all, these HPHCs contribute to human disease is the ultimate issue. The level of available evidence, both with regards to specific populations and the general population as a whole, will be reviewed here

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[191] Lisko et al., *supra* note 136; Barrett H. Raymond, Katreena Collette-Merrill, Roger G. Harrison, Sabrina Jarvis & Ryan Jay Rasmussen, *The Nicotine Content of a Sample of E-Cigarette Liquid Manufactured in the United States*, 12 J. ADDICTION MED.127, 127 (2018).

[192] Maciej L. Goniewicz, Ribhav Gupta, Yong Hee Lee, Skyler Reinhardt, Sungroul Kim, Bokyeong Kim, Leon Kosmider & Andrzej Sobczak, *Nicotine Levels in Electronic Cigarette Refill Solutions: A Comparative Analysis of Products from the U.S., Korea, and Poland*, 26 INT'L J. DRUG POL'Y 583 (2015).

[193] Raymond et al., *supra* note 191, at 127.

[194] Requirements for Tobacco Product Manufacturing Practice, 88 Fed. Reg. 15,174 (Mar. 10, 2023) [hereinafter TPMP Proposed Rule].

[195] *See, e.g.*, U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY—QUALITY SYSTEMS APPROACH TO PHARMACEUTICAL CGMP REGULATIONS (Sept. 2006), https://www.fda.gov/media/71023/download.

[196] TPMP Proposed Rule, *supra* note 194, at 15,175.

[197] *Id.* at 15,179–80.

with the understanding that it is difficult to impossible to prove a product *does not* cause a disease or condition using empirical scientific methods.

1. In General

Whereas there is ample evidence that use of combustible tobacco products increases mortality and decreases life expectancy, no such long-term data exist for ENDS products. Of course, an absence of evidence does not equate to evidence of an absence: a longitudinal cohort study would be required to confidently conclude, with a reasonable degree of scientific certainty, that use of ENDS products cause less mortality (and morbidity) than use of combustible tobacco products. Whether such a cohort study will ever be completed is, unfortunately, an open question at this time. A search of clinicaltrials.gov with the keyword "E-cigarette" (last on January 22, 2023) resulted in 498 trials, none of which represents a prospective cohort study large enough to potentially answer the question, "does ENDS product usage increase one's mortality risk?"

The largest and longest prospective cohort study to date is the Population Assessment of Tobacco and Health (PATH) Study,[198] an ongoing nationally representative, longitudinal survey beginning in 2013 that tracks, among other things, self-reported cardiovascular disease outcomes such as myocardial infarction, bypass surgery, stroke, and heart failure diagnoses related to tobacco use. At this time, data from Waves 1 through 6 are available, representing data collected between 2013 and 2021.[199] One study from Wave 5 contained data from 24,027 individuals, including 822 exclusively ENDS product users, 6,515 exclusively combustible tobacco product users, and 1,858 dual users.[200] The surveys found an approximately 34% relative risk reduction of all cardiovascular disease between exclusively ENDS product users and exclusively combustible tobacco product users.[201] Moreover, the authors found no difference in cardiovascular risk between exclusively ENDS product users and non-users of tobacco products altogether.[202] Limitations of this study primarily are concerned with the self-reported aspects of the outcome measures, as well as its still-limited duration of follow up, meaning that even the PATH study is currently unable to answer the question "does ENDS product usage increase one's mortality risk?" to a reasonable degree of scientific certainty.

Additionally, Public Health England (an executive agency within the Department of Health and Social Care in England) has periodically commissioned reports to review existing literature, surveys, and databases related to ENDS product use and to summarize the relative harms of ENDS products versus combustible tobacco products. The most recent report published in 2018 cited one assessment of published data that concluded that "the cancer potencies of e-cigarettes were largely under 0.5% of the risk of smoking" and "[c]omparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of

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[198] *Population Assessment of Tobacco and Health: A Collaboration Between the NIH and FDA*, PATHSTUDYINFO.NIH.GOV, https://pathstudyinfo.nih.gov/ (last visited June 9, 2023).

[199] *Population Assessment of Tobacco and Health (PATH) Study*, Nat'l Inst. on Drug Abuse, https://nida.nih.gov/research/nida-research-programs-activities/population-assessment-tobacco-health-path-study (last visited June 9, 2023).

[200] Berlowitz et al., *supra* note 70, at 1557.

[201] *Id.* at 1557–58.

[202] *Id.*

smoking."[203] In fact, Public Health England goes as far as publicizing to its citizens that ENDS products are "around 95% safer than smoking."[204] Moreover, England's Ministry of Health announced its "Swap to Stop" campaign in which it will mail one million vape starter kits to adult smokers in 2023 in an effort to decrease combustible use.[205] A recent umbrella review (i.e., a tertiary review of the secondary literature including seven systematic reviews totaling 183 primary studies and reports) concluded that although ENDS products do cause an increase in overall cardiovascular risk, they may represent a "temporary lesser evil" than traditional combustible cigarettes in a risk reduction or risk modification strategy, but there were no attempts at quantifying the risk levels.[206]

In the absence of definitive morbidity and mortality data obtained during tobacco product development programs and limited data from post-market surveillance due to agency failures to setup a functional regulatory system, epidemiological modeling, while imperfect, has stepped in to attempt to predict the life-saving potential of ENDS products as a substitute for combustible products. One group of researchers created a model based on 2013 use patterns (i.e., uptake, cessation, and co-use of combustibles relative to ENDS products), and estimated that by 2060, 1.8 million deaths could be prevented and 38.9 million life years could be gained if ENDS products remained as used in 2013.[207] This was also based on the assumption that ENDS products were 95% less harmful than combustible alternatives.[208] Another group of researchers used the Population Health Impact Model (which enabled them to modify variables such as the relative risk of ENDS products to combustible tobacco products, quitting rate, initiation rate, and proportion smoking after ten years) to estimate that, based on modeling between 1991 and 2040, somewhere between 760,000 and 2.52 million deaths could be prevented by substituting ENDS products for combustible tobacco products.[209]

FDA is also interested in consumer use patterns related to new ENDS products, particularly co-use and/or switching to combustible products. As such, it requests that manufacturers filing a PMTA for an ENDS product summarize (but not necessarily conduct de novo research) the likelihood that consumers will adopt the new tobacco product and then switch to other tobacco products that may present higher levels of risk, such as cigarettes; the likelihood of consumers using the new tobacco product in

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[203] ANN MCNEILL, LEONIE S. BROSE, ROBERT CALDER, LINDA BAULD & DEBBIE ROBSON, PUB. HEALTH. ENG., EVIDENCE REVIEW OF E-CIGARETTES AND HEATED TOBACCO PRODUCTS 2018—A REPORT COMMISSIONED BY PUBLIC HEALTH ENGLAND 19 (2018), https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf.

[204] *Id.* at 20, 175.

[205] Press Release, U.K. Gov't, Smokers Urged to Swap Cigarettes for Vapes in World First Scheme (Apr. 11, 2023), https://www.gov.uk/government/news/smokers-urged-to-swap-cigarettes-for-vapes-in-world-first-scheme (last visited June 11, 2023) [hereinafter Press Release, U.K. Gov't].

[206] Mariangela Peruzzi, Giuseppe Biondi-Zoccai, Roberto Carnevale, Elena Cavarretta, Giacomo Frati & Francesco Versaci, *Vaping Cardiovascular Health Risks: An Updated Umbrella Review*, 8 CURRENT EMERGENCY & HOSP. MED. REPS. 103, 103 (2020).

[207] Levy et al., *supra* note 74, at 6, 8.

[208] *Id.* at 6.

[209] Peter N. Lee, John S. Fry, Stanley Gilliland, III, Preston Campbell & Andrew R. Joyce, *Estimating the Reduction in US Mortality if Cigarettes Were Largely Replaced by E-Cigarettes*, 96 ARCHIVES TOXICOLOGY 167, 167 (2022).

conjunction with other tobacco products; and an assessment of abuse liability (i.e., the addictiveness, abuse, and misuse potential of the new tobacco product and the exposure to nicotine during product use).[210]

2. Specific Populations

As enumerated in the TCA, FDA has been directed to consider two specific populations when making its determination on whether an ENDS product is APPH: 1) current non-users of tobacco products and 2) current users of combustible tobacco products.

i. Current Non-Users of Tobacco Products

The ENDS PMTA Guidance recommends that applicants address the likelihood, based on the research information contained in the application, that current nonusers of tobacco products will initiate or reinitiate tobacco use with the new tobacco product.[211] Although not explicitly stated, the risk or potential harms that FDA is ostensibly worried about is that new ENDS product users would transition to dual use or eventually switch to exclusive use of combustible tobacco products. Thus, the most salient research for the purpose of creating product standards are those studies that focus on the endpoint of combustible tobacco product dependence.

Indeed, ENDS product use has been shown to precede conventional combustible tobacco product use: in a systematic review and meta-analysis covering 17,389 adolescents and young adults aged fourteen to thirty years old, ENDS product users had a 3.50 times greater likelihood of initiating cigarette smoking compared to those who never tried ENDS products (23% vs. 7%).[212] Based on cross-sectional study design, however, it is difficult to tease out the potential psychosocial confounding variables (i.e., finding those individuals who would have initiated cigarette smoking even without ENDS products availability). Researchers also assume an unlikely policy vacuum: if FDA were to promote a transition from combustible tobacco to ENDS products, the agency would likely undertake further concurrent actions to discourage and disincentivize combustible tobacco product use.

The most detailed attempt to identify and control for other psychosocial variables of combustible tobacco initiation was published in 2017 by Dutra and Glantz.[213] They found that in applying the psychosocial model of smoking, including demographic characteristics, living with a smoker, willingness to wear clothing with a tobacco logo, likelihood of smoking cigarettes from a friend, and use of tobacco products other than cigarettes or ENDS products, their model categorized less than 25% of 6th to 12th grade ENDS-product-only users as users of combustible cigarettes.[214] Accordingly, the authors concluded that based on historic trends in the NYTS, the introduction of ENDS products was not associated with the linear decline in cigarette smoking amongst youth.

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[210] ENDS PMTA GUIDANCE, *supra* note 89, at 25–27.

[211] *Id.* at 26, 41.

[212] Soneji et al., *supra* note 77, at 788, 794.

[213] Lauren M. Dutra & Stanton A. Glantz, *E-Cigarettes and National Adolescent Cigarette Use: 2004–2014*, 139 PEDIATRICS 1 (2017).

[214] *Id.* at 1.

Numerically, the most recent data from NYTS suggest that 11.3% of high school students (approximately 1.7 million nationwide) and 2.8% of middle school students reported use of ENDS products (defined as at least once in the last thirty days) in 2021, of whom approximately 40% use ENDS products twenty to thirty days per month.[215] However, lacking in the public health literature is a hypothesis of which specific youth populations will transition from an exclusive ENDS product user to a user of combustible tobacco products, as well as when and how such a transition might occur. Thus, it is an open question as to the full scale and scope of long-term health impacts that will be felt by this population—partially because the long-term risks of ENDS products are not yet completely elucidated and partially because it is unknown how many of them will transition to dual use or exclusive use of combustible tobacco products later in their lives, especially if FDA subsequently revokes an ENDS product marketing authorization after users have grown accustomed to it.

It is important to note that youth and other tobacco-naïve individuals are not the only population at risk. Former smokers who have successfully quit cigarette smoking have also been found to initiate ENDS product use. Data from the National Health Interview Survey showed that the prevalence of ENDS product use amongst former adult smokers increased from 4.2% in 2017 to 5.5% in 2018.[216] Extrapolated to the population level, this equates to approximately 3.4 million former cigarette smokers who used an ENDS product in 2018.[217] Again, it is unknown how many, if any, of these ENDS product users have or will transition back to combustible tobacco product use, making them another vulnerable population.

ii. Current Users of Combustibles

Current combustible users, on the other hand, are the population for whom harm reduction is intended. The most recent survey data showed that in 2020, approximately 12.5% of the adult population (or 30.8 million people) were active cigarette smokers, as defined by consumption of more than 100 cigarettes in their lifetime and current every day or nearly every day smoking.[218] The ENDS PMTA Guidance requests applicants discuss "the likelihood, based on the research information contained in your application, of current tobacco product users switching to the product instead of ceasing tobacco product use or using an FDA-approved tobacco cessation product" (because use of ENDS products includes inherent risk above quitting altogether or the use of an FDA-approved nicotine replacement therapy (NRT)).[219] Understanding this population and obtaining these data are much more feasible using real-world conditions as compared to the study of current non-users. For example, it is much easier to randomize current smokers to NRT, ENDS products, or placebo than it is to randomize non-smokers to one world in which ENDS products are accessible and one

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[215] Gentzke et al., *supra* note 66, at 1–2, 20.

[216] Wei Bao, Buyun Liu, Yang Du, Linda G. Snetselaar & Robert B. Wallace, *Electronic Cigarette Use Among Young, Middle-Aged, and Older Adults in the United States in 2017 and 2018*, 180 JAMA INTERNAL MED. 313, 314 (2020).

[217] Calculation based on the 2018 U.S. population (approximately 327 million) and the prevalence of former smokers in the population (approximately 20.9%). *See* OFF. OF THE SURGEON GEN., PUB. HEALTH SERV., U.S. DEP'T OF HEALTH & HUM. SERVS., SMOKING CESSATION: A REPORT OF THE SURGEON GENERAL 43 (2020), https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-report.pdf.

[218] Cornelius et al., *supra* note 38.

[219] ENDS PMTA GUIDANCE, *supra* note 89, at 26.

in which they are not. Thus, the quality of potential evidence (by virtue of having, amongst other trial designs, prospective randomized controlled trials) is higher for this sub-population.

The majority (approximately 77% in the largest, most recent survey) of current users of ENDS products currently or previously used combustible cigarettes.[220] Multiple surveys have revealed that these users view ENDS products as a means to quit combustible product use or reduce the risk of tobacco-related health harms.[221] For example, in a survey taken in 2013 in which ENDS product users were given multiple choices for why they use the products, there was greater interest in using them for combustible tobacco product cessation rather than to circumvent clean indoor air laws or out of curiosity/novelty.[222] As discussed previously, and although it confounds the PMTA authorization process with the CDER drug approval process, ENDS products are beginning to show at least comparable (if not increased) effectiveness at promoting complete cessation compared to NRT and with comparable safety profiles.

3. With Regards to Flavored Products

On a single day in late August 2021, FDA issued MDOs for over 55,000 products, all of which were flavored ENDS products (with the exception of tobacco and menthol flavored products).[223] In the following weeks, more MDOs were issued for flavored products and, to date, no flavored ENDS product has been authorized for sale. This led to several flavored ENDS product manufacturers filing lawsuits against FDA to stay the MDOs, alleging that FDA was prohibiting flavored products as a class, rather than adjudicating PMTAs on an application-by-application basis.[224] The plaintiffs argue that, given the absence of notice and comment regulations or product standards, FDA's ban of flavored products as a class was arbitrary and capricious. To date, four separate federal circuit courts have sided with FDA (the Third, Fifth, and Seventh Circuits and the D.C. Circuit) enforcing the MDOs, except that the Fifth Circuit's decision has been vacated pending an *en banc* review.[225] The Eleventh Circuit, on the

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[220] Margaret Mayer, Carolyn Reyes-Guzman, Rachel Grana, Kelvin Choi & Neal D. Freedman, *Demographic Characteristics, Cigarette Smoking, and E-Cigarette Use Among US Adults*, 3 JAMA NETWORK OPEN 1, 1–3 (2020).

[221] *See* Sara Kalkhoran, Nicholas Alvarado, Maya Vijayaraghavan, Paula J. Lum, Patrick Yuan & Jason M. Satterfield, *Patterns of and Reasons for Electronic Cigarette Use in Primary Care Patients*, 32 J. GEN. INTERNAL MED. 1122, 1122 (2017); Deesha Patel, Kevin C. Davis, Shanna Cox, Brian Bradfield, Brian A. King, Paul Shafer, Ralph Caraballo & Rebecca Bunnell, *Reasons for Current E-Cigarette Use Among U.S. Adults*, 93 PREVENTIVE MED. 14, 14 (2016).

[222] Carla J. Berg, Regine Haardoerfer, Cam Escoffery, Pinpin Zheng & Michelle Kegler, *Cigarette Users' Interest in Using or Switching to Electronic Nicotine Delivery Systems for Smokeless Tobacco for Harm Reduction, Cessation, or Novelty: A Cross-Sectional Survey of US Adults*, 17 NICOTINE & TOBACCO RSCH. 245, 245 (2015).

[223] Press Release, U.S. Food & Drug Admin., FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health (Aug. 26, 2021), https://www.fda.gov/news-events/press-announcements/fda-denies-marketing-applications-about-55000-flavored-e-cigarette-products-failing-provide-evidence.

[224] *See, e.g.*, Turning Point Brands, Inc. v. U.S. Food & Drug Admin., No. 21-3855 (6th Cir. filed Sept. 21, 2021); Breeze Smoke, LLC v. U.S. Food & Drug Admin., 18 F.4th 499 (6th Cir. 2021) (denying stay of FDA's MDO because, *inter alia*, PMTA could be denied for failure to show that it would benefit public health enough to outweigh public-health detriment to children) (cert. denied) (Breeze Smoke subsequently voluntarily withdrew its appeal to the Sixth Circuit).

[225] Gripum, LLC v. U.S. Food & Drug Admin., 47 F.4th 553 (7th Cir. 2022) (holding FDA conducted sufficiently individualized review of evidence in denying manufacturer's PMTA); Prohibition Juice Co. v.

other hand, sided with the Petitioners and issued a stay on the MDOs for six manufacturers, pending further review of their PMTAs by FDA.[226] Although the arbitrary and capricious standard of judicial review is deferential to the agency, FDA's conduct in regards to the MDOs for flavored ENDS products, as described in detail below, may in fact rise to that standard. Thus, this circuit split, which may be deepened by the Fifth Circuit's *en banc* panel, may be ripe for Supreme Court review.

These lawsuits hinge on what type and quantity of evidence should be required to prove a product meets the APPH standard. In general, randomized prospective clinical trials are the gold standard for clinical trials and are usually required to prove or invoke causation. Other forms of research such as retrospective analyses or cohort studies carry less evidentiary weight as they are inherently prone to confounding and various form of biases. However, in some settings and for some scientific questions, alternative clinical trial designs, modeling studies, in vitro studies, or some combination of the aforementioned may be appropriate and sufficient for meeting the APPH standard. The TCA's statutory text contemplates this issue. Section 910(C)(5) delineates "well-controlled" studies from other "valid scientific evidence," and allows the latter to be used to demonstrate a tobacco product is APPH if FDA finds such evidence "sufficient."

The ENDS PMTA Guidance described what types of non-well-controlled studies would be considered "sufficient." The relevant text of the ENDS PMTA Guidance language is listed below (emphasis added):

> Given the relatively new entrance of ENDS on the U.S. market, FDA understands that limited data may exist from scientific studies and analyses. If an application includes, for example, information on other products (e.g., published literature, marketing information) with appropriate bridging studies, FDA intends to review that information to determine whether it is valid scientific evidence sufficient to demonstrate that the marketing of a product would be APPH. Nonclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health. Nonetheless, in general, FDA ***does not expect that applicants will need to conduct long-term studies to support an application***. As an example for nonclinical assessments, long-term studies such as carcinogenicity bioassays are not expected to be included in an application. For clinical assessments, ***instead of conducting clinical***

U.S. Food & Drug Admin., 45 F.4th 8 (D.C. Cir. 2022) (holding that FDA did not exceed its authority under the TCA by requiring manufacturers to show their products carried sufficiently greater benefits than non-flavored liquid products; FDA did not misdirect manufacturers about evidence required to demonstrate products were appropriate for protection of public health; and denial of applications was not arbitrary and capricious); Liquid Labs LLC v. U.S. Food & Drug Admin., 52 F.4th 533, 540 (3d Cir. 2022) (finding that FDA did not provide inadequate notice, upset any reliance expectations, or act arbitrarily or capriciously when it rejected certain of plaintiff's evidence submitted as part of its PMTA). *But see* Wages & White Lion Invs., L.L.C. v. U.S. Food & Drug Admin., 58 F.4th 233 (5th Cir. 2023) (vacating the circuit court's denial of a marketer's petition to stay the MDO (finding FDA did not act arbitrarily in concluding that a marketer's survey was insufficient to show a benefit to adult smokers, as required for approval of PMTAs (41 F.4th 427) and granting a rehearing by the court *en banc*).

[226] Bidi Vapor LLC v. U.S. Food & Drug Admin., 47 F.4th 1191 (11th Cir. 2022) (finding FDA's actions arbitrary and capricious without considering companies' marketing and sales-access-restriction plans designed to minimize youth exposure and access).

> ***studies that span months or years to evaluate potential clinical impact, applicants could demonstrate possible long-term health impact by including existing longer duration studies in the public literature with the appropriate bridging information (i.e., why the data used are applicable to the new tobacco product) and extrapolating from short-term studies.*** In addition, nonclinical in vitro assays that assess the toxicities that are seen following long-term use of tobacco products may be supportive of these clinical assessments. These studies, used as a basis to support a PMTA, should be relevant to the new tobacco product and address, with robust rationale, acute toxicological endpoints or other clinical endpoints that may relate to long-term health impacts.[227]

With regards to flavored ENDS products, FDA has focused on the risk to a specific sub-population (children, as emphasized by FDA's attention to studies in middle school and high school aged subjects).[228] In its MDO decision letters, FDA functionally subsequently required that PMTA applicants show that the benefit of the product (by virtue of getting adult combustible users to switch to flavored ENDS products) outweighed the risks of increased uptake in the youth population. This could be achieved, in theory, by conducting a bridging study that shows that the flavored ENDS product was similar enough to the non-flavored ENDS products that have been shown to decrease combustible use in adults.

The main controversy in the four flavored-product lawsuits identified above is what type of study the bridging study should be. Prior to issuing any of the litigated MDOs, FDA stated that it did "not expect that long-term clinical studies will need to be conducted for each PMTA; instead, it expects that it should be able to rely on other valid scientific evidence to evaluate some PMTAs" in its Final Rule on all PMTAs.[229] Thus, many flavored ENDS product companies relied on FDA's stated position that it did "not expect that applicants will have to conduct long-term studies to support an application" and did not perform or submit such evidence. However, in its MDO decision letters, FDA found that these non-clinical bridging studies were insufficient, leading the plaintiffs to accuse FDA of performing a "surprise switcheroo" that therefore rose to the level of arbitrary and capricious adjudications.[230]

FDA's approach in regulating flavored ENDS products has drawn significant scrutiny. First and foremost, plaintiffs raised the "surprise switcheroo" argument after learning in discovery of internal memoranda that were circulated within FDA in July and August of 2021 (two years after FDA issued the public-facing ENDS PMTA Guidance block quoted, *supra*). In these memoranda, the agency appears to take a

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[227] ENDS PMTA GUIDANCE, *supra* note 89, at 13–14 (footnotes omitted).

[228] *See* Press Release, U.S. Food & Drug Admin., FDA Finalizes Enforcement Policy on Unauthorized Flavored Cartridge-Based E-Cigarettes that Appeal to Children, Including Fruit and Mint (Jan. 2, 2020), https://www.fda.gov/news-events/press-announcements/fda-finalizes-enforcement-policy-unauthorized-flavored-cartridge-based-e-cigarettes-appeal-children. *See also Breeze Smoke, LLC*, 18 F.4th at 505 ("As of 2020, 84.7% of high school ENDS users and 73.9% of middle school ENDS users reported using flavored products. FDA Review of Breeze Smoke's Application, A12. And according to one study, over 80% of children aged 12–17 said that their first experience with ENDS involved a flavored product.").

[229] Premarket Tobacco Product Applications and Recordkeeping Requirements, 86 Fed. Reg. 55,300, 55,387 (Oct. 5, 2021) (codified at 21 C.F.R. §§ 1100, 1107, 1114).

[230] *See, e.g.*, Wages & White Lion Invs., L.L.C. v. Food & Drug Admin., 41 F.4th 427, 435 (5th Cir. 2022), reh'g en banc granted, opinion vacated, 58 F.4th 233 (5th Cir. 2023).

position at odds with its statements in the ENDS PMTA Guidance by saying that bridging studies for flavored ENDS products would have to be product-specific randomized controlled trials or longitudinal cohort studies, two of the most burdensome and lengthy studies to conduct.[231] The agency even went so far as to say that the absence of these burdensome studies would be a "fatal flaw" for any flavored ENDS PMTA application.[232] Arguably, this would constitute a binding norm that, per administrative law precedence, must undergo notice and comment rulemaking.[233] The public deserves to know (and participate in crafting) the requirements for authorization for ENDS products. As these cases illustrate, the authorization standards were not issued prospectively in the form of guidance or regulations. Rather, they have been propounded in the MDO letters (which are not made publicly available[234])—or even worse, via internal FDA memoranda. This essentially means FDA is issuing its product standards in each agency action on individual products and subsequent arguments/ briefs presented in federal court. Thus, reviewing courts may end up defining the APPH standard as an issue of substantive law, rather than FDA via the rulemaking process that is the cornerstone of administrative law.[235]

Indeed, the Fifth Circuit rejected FDA's approach in its March 2023 decision regarding the MDO that R.J. Reynolds Vapor Company received for its menthol-flavored ENDS products.[236] The court scrutinized the Fatal Flaw memo as an impermissible deviation from the APA's notice-and-comment requirements.[237] FDA argued that the Fatal Flaw memo was a general statement of policy that was exempt from notice-and-comment requirements, but the court found that it was a substantive rule because the agency intended to bind itself to the legal position therein.[238] Specifically, the court pointed to the Fatal Flaw memo's requirement that applicants include the "necessary" types of studies (to wit, RCTs or longitudinal cohort studies) in addition to how FDA has acted in general (the "myriad" MDOs based on the same

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[231] *See* Emergency Application for a Stay of Agency Order Pending the Disposition by the U.S. Court of Appeals for the Sixth Circuit of a Petition for Review and Any Further Proceedings in the Supreme Court at 13–14, *Breeze Smoke, LLC*, 18 F.4th (Nov. 23, 2021), https://www.supremecourt.gov/DocketPDF/21/21A176/201205/20211123170816540_1%20-%20Breeze%20Smoke%20-%20Stay%20Application.pdf.

[232] Alex Norcia, *FDA Memos Reveal Its "Fatal Flaw" Rejection Plan for Flavored Vapes*, FILTER (Nov. 3, 2021), https://filtermag.org/fda-memos-flavored-vapes/.

[233] *See generally* Ronald M. Levin, *Rulemaking and the Guidance Exemption*, 70 ADMIN. L. REV. 263, 356–57 (2018) (discussing the "binding norms" test, including Pac. Gas & Electric Co. v. Fed. Power Comm'n, 506 F.2d 33 (D.C. Cir. 1974); Nat'l Mining Ass'n v. McCarthy, 758 F.3d 243, 253 (D.C. Cir. 2014); American Bus Ass'n v. United States, 627 F.2d 525 (D.C. Cir. 1980)).

[234] *Tobacco Product Marketing Orders*, U.S. FOOD & DRUG ADMIN. (July 10, 2023), https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/tobacco-products-marketing-orders (listing only a "Sample Decision Summary Document" under Marketing Denial Orders) (last visited June 17, 2023).

[235] *See* James Hunnicutt, *Another Reason to Reform the Federal Regulatory System: Agencies' Treating Nonlegislative Rules As Binding Law*, 41 B.C. L. REV. 153, 158 (1999) (reinforcing that "the key elements of informal rulemaking—also known as 'notice-and-comment'—are that before issuing a legislative rule, an agency must notify the public of the proposed rule, accept commentary on the proposal and respond to that commentary").

[236] R.J. Reynolds Vapor Co. v. U.S. Food & Drug Admin., 65 F.4th 182 (5th Cir. 2023).

[237] *Id.* at 193.

[238] *Id.* (quoting Texas v. Equal Emp. Opportunity Comm'n, 933 F.3d 433, 441 (5th Cir. 2019); Syncor Int'l Corp. v. Shalala, 127 F.3d 90, 94 (D.C. Cir. 1997)).

deficiencies identified as "fatal" in the memo).[239] The language used in the Judge Jones opinion was not subtle in its critique of FDA's approach as a product regulator.[240] This Fifth Circuit panel granted R.J. Reynolds an emergency stay on the MDO for its menthol products, with the full merits phase of the case being deferred until its *en banc* consideration of these similar arguments in the non-menthol flavored ENDS case.[241]

C. Marketing

CTP has also been tasked with reviewing the marketing plans for ENDS products, particularly as they relate to targeting potential youth users. This enforcement power was asserted prior to the issuance of any ENDS product marketing authorization, as FDA's attention was drawn to marketing strategies for flavored ENDS products that were targeting youth in late 2017. After an investigation, FDA issued seventeen warning letters in May 2018 to manufacturers, distributors, and retailers for selling e-liquids with labeling and/or advertising that resembled kid-friendly food products, such as juice boxes, candy, or cookies.[242] In the summer of 2018, FDA conducted an undercover investigation of both online and brick-and-mortar retailers and issued more than 1,300 warning letters and civil money penalties (CMP) to retailers who illegally sold ENDS products to minors.[243] FDA also issued twelve warning letters to online retailers that were selling misleadingly advertised and/or e-liquids flavored to resemble child-friendly food products (e.g., cookies or candy).[244]

In September of 2018, FDA additionally asked five major ENDS product makers to propose a set of safeguards that they could implement to limit minors' access to ENDS products sold both online and in brick-and-mortar stores.[245] These five manufacturers were, at the time, allowed to keep their products on the market because FDA exercised enforcement discretion, as discussed *supra* in Section III.B. Due to FDA's concern about youth vaping, it threatened to revoke that discretion and pull these ENDS products from the market if the manufacturers did not provide a "written response that included a detailed plan, including specific timeframes, to address and mitigate widespread use by minors."[246] Industry responded with several potential safeguards, including:

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[239] *Id.* at 193.

[240] *Id.* (calling FDA's argument that the Fatal Flaw memo was not a substantive rule "not a close call"); *id.* at 190 ("The FDA inexplicably switched its position . . . ."); *id.* at 191 ("The FDA's disregard for the principles of fair notice and consideration of reliance interests is exacerbated by its failure to consider alternatives to denial.").

[241] *See* Wages & White Lion Invs., L.L.C. v. Food & Drug Admin., 41 F.4th 427 (5th Cir. 2022), reh'g en banc granted, opinion vacated, 58 F.4th 233 (5th Cir. 2023); *supra* note 230, and accompanying text. *See generally* Jim McDonald, *Vaping Companies vs FDA: Appeals and Legal Actions*, VAPING360 (June 16, 2023), https://vaping360.com/vape-news/111563/vape-companies-challenging-fda-marketing-denials/ (last visited June 17, 2023).

[242] FDA, ENFORCEMENT PRIORITIES, *supra* note 93, at 6.

[243] *Id.* at 6–7.

[244] *Id.* at 7.

[245] *CTP Letters to Industry: Letters to Manufacturers Regarding Plans to Address Youth Access and Use*, U.S. FOOD & DRUG ADMIN. (Sept. 12, 2018), https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/ctp-letters-industry#youth-access.

[246] *See, e.g.*, Letter from Scott Gottlieb, Comm'r, U.S. Food & Drug Admin., to Kevin Burns, JUUL Labs, Inc. (Sept. 12, 2018), https://www.fda.gov/media/119669/download.

- Establishing or enhancing programs, such as mystery shopper programs, to monitor retailer compliance with age-verification and sales restrictions;
- Establishing and enforcing contractual penalties for contracted retailers that sell tobacco products to youth;
- Using age-verification technology to better restrict access to the manufacturer's website, such as through independent, third-party age- and identity-verification services that compare customer information against third-party data sources; and
- Limiting the quantity of ENDS products that a customer may purchase within a given period of time.[247]

In its premarket tobacco product marketing granted orders for Vuse, NJOY, and all other ENDS products to date, FDA made it clear that the burden of implementing these programs and reporting on their productivity remains with the companies, and such companies must issue subsequent reports to FDA regarding their efficacy.[248]

However, FDA's attention to marketing is not limited to youth. It sent a warning letter to JUUL in September 2019 regarding the following statements directed at adults who use combustible tobacco products:

> "'[JUUL is] a smart, really well thought-out alternative to smoking.' Make the switch."
>
> "I think [JUUL is] an amazing invention . . . I don't know how we lived without that. The alternative for adult smokers."
>
> "Elimination of combustible cigarettes is crucial to reduce risk of harm"
>
> "Improve the lives of the world's one billion adult smokers"[249]

With then-Acting FDA Commissioner Ned Sharpless remarking that, "[r]egardless of where products like e-cigarettes fall on the continuum of tobacco product risk, the law is clear that, before marketing tobacco products for reduced risk, companies must demonstrate with scientific evidence that their specific product does in fact pose less risk or is less harmful. JUUL has ignored the law . . . ."[250] Of note, FDA made the decision that ENDS products would not be allowed to apply for the "modified risk" marketing authorization unless and until a predicate ENDS product was approved via the PMTA pathway in 2016.[251] For comparison, as discussed *supra* Section III.C. Public Health England stated the year prior that it was no longer going to censure these types of statements from ENDS product makers, and would in fact be promoting

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[247] FDA, ENFORCEMENT PRIORITIES, *supra* note 93, at 7.

[248] *See, e.g.*, FDA, TPL REVIEW, *supra* note 141, at 4–5 (stating "FDA has included such restrictions in MGOs issued to date"; this TPL Review is, currently, the most recent MGO granted).

[249] Press Release, U.S. Food & Drug Admin., FDA Warns JUUL Labs for Marketing Unauthorized Modified Risk Tobacco Products, Including in Outreach to Youth (Sept. 9, 2019), https://www.fda.gov/news-events/press-announcements/fda-warns-juul-labs-marketing-unauthorized-modified-risk-tobacco-products-including-outreach-youth (describing the warning letter sent to JUUL and disclosing the source of the quoted text as JUUL's "Make the Switch" campaign and "Switching Program" presentation to the Cheyenne River Sioux Tribe).

[250] *Id.*

[251] *Supra* notes 111–14 and accompanying text.

statements like "vaping is at least 95% less harmful than smoking."[252] Moreover, Public Health England announced in April 2023 that it would mail ENDS products directly to one million adult smokers in its "Swap to Stop" campaign.[253] By prohibiting fact-based statements regarding the relative risk of ENDS products, FDA is contributing to public confusion and misperceptions about these products.

FDA's Marketing Granted Order letter for the Vuse series of products issued to R.J. Reynolds Vapor Company in October 2021 makes clear how important marketing limitations were, especially for advertisements that might be directed at youth, in the agency's determination that a product is APPH. In its initial Marketing Granted Order letter dated October 12, 2021, FDA made authorization contingent upon R.J. Reynolds Vapor Company's satisfaction of various requirements, which included, *inter alia*, a post-market reporting requirement of any subsequent creative briefs or paid media plans, including plans to employ any partners, influencers, bloggers, or brand ambassadors, especially as they relate to certain target audiences by age (especially twenty-one to twenty-four years old); a summary of media tracking and optimization by audience demographics (including age); and an analysis of actual delivery of advertising impressions by audience demographics (including age).[254]

V. RECOMMENDATIONS ON MODEL ENDS PRODUCT STANDARDS

A. Learning Lessons from FDA's Prior Actions

From FDA's limited authorizations of ENDS PMTAs, to date, it is clear that ENDS products can be APPH (for example, Vuse and NJOY).[255] However, these authorizations have been limited to tobacco-flavored products—to date, no other flavored ENDS product has been authorized, all non-menthol flavored products have been issued MDOs,[256] and a decision on menthol-flavored products (both ENDS[257] and combustibles[258]) is expected soon. Regarding the main active ingredient in ENDS

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[252] Press Release, Public Health England, *supra* note 115.

[253] Press Release, U.K. Gov't, *supra* note 205.

[254] *See, e.g.*, U.S. FOOD & DRUG ADMIN., MARKETING GRANTED ORDER LETTER FOR R.J. REYNOLDS VAPOR CO., PM0000551, PM0000553 & PM0000560 12–15 (Oct. 12, 2021), https://www.fda.gov/media/153010/download.

[255] *See generally* Kenneth E. Warner, Karalyn A. Kiessling, Clifford E. Douglas & Alex C. Liber, *A Proposed Policy Agenda for Electronic Cigarettes in the US: Product, Price, Place, and Promotion*, 41 HEALTH AFFS. 1299, 1301–03 (2022).

[256] *Premarket Tobacco Product Marketing Granted Orders*, U.S. FOOD & DRUG ADMIN. (June 14, 2023), https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-granted-orders (noting all listed authorizations for ENDS products are for tobacco-flavored products) (last visited June 17, 2023).

[257] Steve Ellwanger, *FDA Deals Regulatory Blow to Menthol-Flavored E-Cigarettes*, MKTG. DAILY (Oct. 28, 2022), https://www.mediapost.com/publications/article/379253/fda-deals-regulatory-blow-to-menthol-flavored-e-ci.html.

[258] Press Release, U.S. Food & Drug Admin., FDA Proposes Rules Prohibiting Menthol Cigarettes and Flavored Cigars to Prevent Youth Initiation, Significantly Reduce Tobacco-Related Disease and Death (Apr. 28, 2022), https://www.fda.gov/news-events/press-announcements/fda-proposes-rules-prohibiting-menthol-cigarettes-and-flavored-cigars-prevent-youth-initiation; Tobacco Product Standards for Menthol in Cigarettes, 87 Fed. Reg. 26,454 (proposed May 4, 2022) (to be codified at 21 C.F.R. pt. 1162).

products, 6% nicotine concentration and below in the e-liquid has been authorized.[259] However, a more clinically meaningful exposure standard can and should be created in consultation with public health officials and industry. For example, a 6% concentrated e-liquid can result in drastically different serum concentrations in the user based on other product specifications, such as coil heat and puff topography.[260] Thus, a more specific exposure standard(s) should be established. This will have the added benefit of helping the United States transition from a country with a tobacco addiction to one with a nicotine addiction, should the country wish to subsequently ban combustible products as other countries such as New Zealand have done.[261]

Similarly, HPHCs are amenable to an objective and quantifiable cutoff. Like nicotine, the quantity of each HPHC can be elucidated in the aerosols delivered to the user via well-established scientific methods (mass spectroscopy and gas chromatography).[262] Moreover, these methods can identify any previously unknown HPHC that can be found in the aerosol, regardless of the presence of an HPHC in the e-liquid.[263] Tailoring the product standards for ENDS products to the aerosol has two distinct advantages. First, it would obviate the need for regulatory micromanagement the of other aforementioned engineering components, such as the material and power of the heating coil and the materials used in the cartridges or containers.[264] Second, the aerosol is the more clinically meaningful entity, as it is the substance to which the user is actually exposed. Should ENDS products subsequently be linked to a specific disease state in epidemiologic studies, the contents of the aerosolized product would be the most meaningful target to study scientifically.

Another emerging theme from ENDS product authorizations is that showing proof of marketing limitations and point-of-sale purchase limitations (i.e., protecting youth) can help establish that a product is APPH, independent of the chemical properties of the ENDS product. FDA spent significant length in its authorization letters for Vuse and NJOY explaining that authorization was conditioned upon the marketing and sales restrictions for youth.[265] Marketing and point-of-sale restrictions will primarily be the responsibility of product makers with post-market reporting requirements on their efficacy to FDA for continued oversight.

B. Enshrining Harm Reduction into the APPH Framework

The TCA implemented a brand new authorization standard (APPH) for FDA to interpret.[266] The statutory language departed from the safety/efficacy or risk/benefit standard commonly used at FDA for other products, such as pharmaceuticals and biologics, for a reason: tobacco and tobacco-derived products are inherently unsafe. This should be relevant to how FDA frames the burden of proof for its PMTA applicants. Applicants should not have to prove that ENDS products are safe (i.e.,

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[259] FDA, TPL REVIEW, *supra* note 141 (Marketing Granted Order for 6% nicotine ENDS product).

[260] *See supra* notes 135–38 and accompanying text.

[261] *See generally* Chris McCall, *A Smoke-Free Generation: New Zealand's Tobacco Ban*, 399 LANCET 1930 (May 21, 2022).

[262] *See supra* note 147 and accompanying text.

[263] Wagner et al., *supra* note 153.

[264] *See supra* Section IV.A.2 and accompanying notes.

[265] FDA, TPL REVIEW, *supra* note 141, at 5–7, 25, 28.

[266] FDCA § 907(a)(3)(B)(i), 21 U.S.C. § 387g(3)(B)(i).

comparing ENDS product users to non-users). They also should not have to prove that they are effective at causing smoking cessation (i.e., a medical treatment for tobacco use disorder) unless they were applying for product approval as a combination drug-device product. Rather, APPH should be interpreted to mean an improvement over the *status quo* in terms of public health: harm reduction should be the primary guiding principle, so long as combustible tobacco products are still an option for consumers.

FDA's proposed analysis as published in Marketing Granted Orders to date is to:

> . . . interpret[] the APPH standard to require a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. In determining whether permitting the marketing of a new tobacco product would result in a net benefit to public health, FDA weighs the potential negative public health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit from adult users of more harmful tobacco products completely switching). . . . In order to show that an ENDS is APPH, an applicant must show that the benefits, including those to adult smokers, outweigh the risks, including those to youth, resulting in a net benefit to the public health.[267]

This is a misconstruction of the APPH standard when looking at the written structure of the statute, as the analysis regarding the population as a whole is a separate and co-equal element to the second two, rather than being a sum of the two:

> i. Considerations. In making a finding described in subparagraph (A), the Secretary shall consider scientific evidence concerning
>
> > I. the risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed standard;
> >
> > 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.[268]

FDA's proposed analysis above over-simplifies the APPH analysis into an X–Y equation (combustible cessation–youth uptake),[269] which is not how the statute constructs the APPH framework.

There are two consequences of this misconstruction of the APPH analysis as consisting of weighing the second two factors to make a sum for the first factor. First, it ignores other public health measures that can protect the public health extrinsic to the total number of users. For example, it fails to consider how banning whole categories of ENDS products (such as flavored products) could lead to an illicit market that would be at risk to exposing users to more dangerous products. It also ignores the potential impact of increasing the legal age of purchase from eighteen to twenty-one

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[267] FDA, TPL REVIEW, *supra* note 141, at 4.

[268] FDCA § 907(a)(3)(B)(i), 21 U.S.C. § 387g(3)(B)(i).

[269] *Supra* note 264 and accompanying text.

years of age, amongst other public health measures that appropriately disproportionately benefit younger potential users. Other measures such as marketing/advertising limitations will also protect former or never users relative to current users of combustible products.

Second, the proposed analysis would create an illusion that the APPH is a numerical, objective standard. If that were the case, it would ostensibly require clinical evidence for every individual product regarding the number of new users of that exact product vs. the number of combustible users who would switch. Generating these numbers would require clinical trials that are either unethical (e.g., randomizing teens to use an ENDS product) or realistically unfeasible (e.g., randomizing people to an environment where the specific ENDS product is commercially available vs. an environment where it is not). Moreover, year-to-year usage data is notoriously finnicky: the drop in high school and middle school ENDS product usage in the 2021 iteration of the NYTS survey was attributed to schools switching from in-person to remote and other pandemic-specific factors.[270]

Another pernicious aspect of FDA's analysis of the APPH standard, to date, is that it explicitly mentions flavored products in their review of tobacco-flavored ENDS PMTAs, as if to negotiate about the harms of flavored products while authorizing tobacco-flavored products.[271] This is constructing a strawman argument: it seems to indicate that flavored products are a reference standard rather than a new product whose PMTA required de novo review. Rather, FDA could and should use combustible tobacco products as the reference standard, as those products were explicitly allowed by the TCA. This would effectively make the APPH framework a harm reduction analysis.

A harm reduction framework for authorization of ENDS products, admittingly, makes less sense when considering adolescents/youth or other current non-users of combustible tobacco products. After all, non-smokers would not be using ENDS products to help them stop using conventional cigarettes or other combustible products. However, ENDS product authorization can still be considered future harm-reducing when considering that any new initiator would be better served by selecting an ENDS product over a combustible product in the first instance. Indeed, while youth use of ENDS products was rising over the past two decades, it was accompanied by a concomitant decline in exclusive combustible use.[272] Moreover, economic research suggests that youth populations will substitute ENDS products for more harmful combustible products based on price.[273]

Regarding the evidentiary burden for PMTA authorization, requiring applicants to conduct long-term clinical studies for each individual product (as was required by the Fatal Flaw memo for flavored ENDS products[274]) should not be necessary. The data on youth use of ENDS products in general lacks evidence regarding morbidity and

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[270] *See supra* note 68 and accompanying text.

[271] *See, e.g.*, FDA, TPL REVIEW, *supra* note 141, at 4–5.

[272] MeLisa R. Creamer, Lauren M. Dutra, Saida R. Sharapova, Andrea S. Gentzke, Kevin L. Delucchi, Ruben A. Smith & Stanton A Glantz, *Effects of E-Cigarette Use on Cigarette Smoking Among US Youth, 2004–2018*, 142 PREVENTIVE MED. 1, 1 (2021).

[273] Rahi Abouk, Charles Courtemanche, Dhaval Dave, Bo Feng, Abigail S. Friedman, Johanna Catherine Maclean, Michael F. Pesko, Joseph J. Sabia & Samuel Safford, *Intended and Unintended Effects of E-Cigarette Taxes on Youth Tobacco Use*, 87 J. HEALTH ECON. 1, 1 (2023).

[274] *See supra* notes 228–38 and accompanying text.

mortality.[275] This is likely due to limitations in the literature regarding how long youth users remain users of ENDS products (and even, in some studies, the risk of future combustible use). These important endpoints are, however, able to be modeled or extrapolated from prior clinical studies.[276] Thus, all that could be required for PMTA authorization is a showing of substantial equivalence in the aerosol contents between a previously authorized ENDS product to establish a plausible basis for harm reduction. Any non-menthol flavor should be considered on a case-by-case basis regarding its relative appeal to youth vs. adults.

Moreover, it is difficult for manufacturers to predict teenagers' use behaviors for a product that is not yet on the market; randomized clinical trials are impossible due to ethical considerations. FDA's answer has been "do a bridging study" without specifics.[277] PMTA review for ENDS products is not a policy lever that could ever completely protect teenagers: even if every single ENDS product was denied, these vulnerable populations could turn to combustible tobacco products or black market alternatives to ENDS products. MDO's are a blunt and imprecise policy tool. Ultimately, the use and availability of the more dangerous combustible products cannot be fully ameliorated by the stringency of regulating ENDS products. That is, no matter how much FDA and public health officials hate combustible products, heavy-handed regulation of ENDS products is unlikely to significantly impact the availability of combustible products.

Thus, it is important both for FDA's APPH analysis and society as a whole that there are extra FDA safeguards in place. Most importantly is the recent ban of sale to persons under the age of twenty-one, which can and should be considered by FDA in its APPH analysis (but, to date, has not been incorporated). Other intoxicating products available for widespread purchase use similar protections for children (i.e., minimum age requirements for purchasing alcohol and cannabis products). These safeguards are considered sufficient to protect these vulnerable populations from these products, while allowing the product to be available to adult users.

VI. CONCLUSION

After reflecting on the first thirteen years of tobacco regulation by FDA, it is clear that the agency's regulation of ENDS products has suffered from significant problems with timeliness and transparency. To date, FDA has failed to balance the differing needs of distinct populations as required in its statutory mandate. In doing so, the agency has largely left behind 35.6 million combustible users who could use an ENDS product to quit or at the very least use a less harmful product.[278]

FDA spent over $500 million in user fees to fund TCORS over the past decade, supporting academic centers that have contributed significantly to the publicly

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[275] *See supra* notes 64–68, 210–12 and accompanying text (noting that endpoints include product use, but not morbidity or mortality).

[276] *See, e.g.*, Levy et al., *supra* note 74.

[277] ENDS PMTA GUIDANCE, *supra* note 89, at 13.

[278] Monica E. Cornelius, Caitlin G. Loretan, Ahmed Jamal, Brittny C. Davis Lynn, Margaret Mayer, Iris C. Alcantara & Linda Neff, *Tobacco Product Use Among Adults—United States, 2021*, 72 MORBIDITY & MORTALITY WKLY. REP. 475, 477 (2023).

available literature on tobacco regulatory science[279] as well as the health risks for important sub-populations.[280] This body of research is ostensibly free from industry bias that has historically plagued the field of tobacco health research. Thus, FDA can and should publish the results of its intramural toxicology research as well as highlighting the TCORS-funded results in support of its product standards.

While FDA has had ample opportunity to gather evidence and work with public health researchers and industry to establish product standards, it has not done so. Instead, the agency has utilized MDOs and litigation as a mechanism to air its approval standards, violating FDA's social contract as a product regulator. The Reagan-Udall Foundation agreed in its December 2022 report on CTP. Amongst its fifteen specific suggestions for improvement was for CTP to issue regulations to "prescribe . . . standards to reduce the need for case-by-case determinations in application reviews."[281] The product standards contained herein would achieve those goals. Additionally, this approach will enshrine harm reduction principles into the APPH standard while balancing the harms to tobacco-naïve youth populations. FDA's current approach to ENDS is inappropriate for the protection of the public health; now is the time for change.

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[279] Joy A. Frechtling et al., *Establishing a Research Base to Inform Tobacco Regulation: Overview*, 7 TOBACCO REGUL. SCI. 144, 144 (2021).

[280] Stephen T. Higgins, Allison N. Kurti, Marissa Palmer, Jennifer W. Tidey, Antonio Cepeda-Benito, Maria R. Cooper, Nicolle M. Krebs, Lourdes Baezconde-Garbanati, Joy L. Hart & Cassandra A. Stanton, *A Review of Tobacco Regulatory Science Research on Vulnerable Populations*, 128 PREVENTIVE MED. 1, 1–2, 15–17 (2019).

[281] REAGAN-UDALL REPORT, *supra* note 4, at 18.