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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2024-N-4085-0001, Advancing Smoking Cessation: FDA and NIH Priorities

The Campaign for Tobacco-Free Kids (Tobacco-Free Kids) submits these written comments in the above-referenced docket, in response to the notice published at 89 Fed. Reg. 77521 (September 23, 2024). Tobacco-Free Kids provided an oral presentation at the public meeting on October 21, 2024.

Fourteen years ago, in August, 2010, public health groups filed a Citizen Petition with the Food and Drug Administration (FDA), calling on the agency to reevaluate its approach to the review and approval of smoking cessation products. Since that Petition, Tobacco-Free Kids and other public health groups have taken every available opportunity to urge FDA to take action to both enhance the effectiveness and usage of approved smoking cessation products and to stimulate innovation in the development of new safe and effective smoking cessation drug therapies.[1] We commend FDA and the National Institutes of Health (NIH) for convening a public meeting on October 21, 2024 to discuss research on, and development of, new smoking cessation products "to stimulate novel product development to reduce the burden of smoking and related chronic illnesses." 89 Fed. Reg. at 77522. We appreciate the opportunity afforded to Tobacco-Free Kids to make comments during the public meeting. We offer these written comments to urge FDA to translate the high-quality discussion occurring at the public meeting into concrete action to help the millions of Americans who smoke to stop smoking and end their nicotine addiction.

I. NATURE OF THE PROBLEM

Although substantial progress has been made over the last 60 years in reducing rates of cigarette smoking, it remains the leading cause of preventable death in the United States, resulting in 480,000 deaths per year.[2] Over 28 million Americans still smoke cigarettes.[3] Moreover, the gains that have been made over the past several decades have not occurred equally for all population groups. Some groups of U.S. adults have higher smoking prevalence than others, including American Indian adults, those who identify as LGBT, those with lower socioeconomic status, those with mental

[1] See, eg, Comments of Campaign for Tobacco-Free Kids in Connection with January 18, 2019 public hearing on "Eliminating Youth Electronic Cigarette and Other Tobacco Product Use: The Role for Drug Therapies," Docket No. FDA-2018-3952 (January 30, 2019) and attached letter from public health groups and cessation researchers to Dr. Scott Gottlieb (December 20, 2018). https://assets.tobaccofreekids.org/content/what_we_do/federal_issues/fda/regulatory/2019_01_30_CTFK_Comments_Eliminating_Youth_EcigUse.pdf

[2] Office of the Surgeon General (OSG), U.S. Department of Health and Human Services (HHS), *The Health Consequences of Smoking - 50 Years of Progress: A Report of the Surgeon General, Executive Summary* 2 (2014), https://www.hhs.gov/sites/default/files/consequences-smoking-exec-summary.pdf.

[3] CDC, "Tobacco Product Use Among Adults—United States, 2021," *MMWR* 72:475-483, May 5, 2023, https://www.cdc.gov/mmwr/volumes/72/wr/pdfs/mm7218a1-H.pdf.

health or substance abuse disorders and those living in the U.S. South or Midwest.[4] Disadvantaged groups are often the targets of tobacco industry marketing, have fewer resources for tobacco cessation treatments and experience financial and other stressors that can lead to continued tobacco use.[5] These disparities contribute to persistent health disparities.[6]

It is beyond dispute that quitting is one of the most important actions that someone who smokes can take to improve personal health. Smoking cessation reduces the risk of developing smoking-related diseases and can add as much as a decade to life expectancy.[7] Despite the known risks of smoking and demonstrable benefits of quitting, far too few smokers are able to quit successfully. In 2022, 68 percent of smokers reported that they want to quit and 53.3 percent of all smokers made a quit attempt that year, but only 8.8 percent had quit within that year.[8] Though studies continue to show higher success in quitting among those who use some form of approved medication,[9] fewer than 2 in 5 smokers use any of those medications when making a quit attempt.[10] Unfortunately, even when cessation medications are used, quit rates are less than optimal, roughly 17 to 33 percent.[11] The *HHS Framework to Support and Accelerate Smoking Cessation 2024*, summarized what has been known for many years: "While most adults who smoke want to quit, and more than half try to quit each year, few successfully quit each year."[12]

Between 1984 and 2006, FDA approved new drug applications (NDAs) for the nicotine patch, gum, lozenge, spray and inhaler (nicotine replacement therapies or NRTs), along with two non-nicotine based therapies, bupropion (ZYBAN and generics) and varenicline (CHANTIX).[13] Most of the existing NRTs have been approved for more than twenty years; as to non-nicotine products, no new medications have been approved in the last eighteen years. Thus, for almost two decades there has been little development and approval of innovative, new smoking cessation products. With approximately 28 million Americans still smoking, the need for more effective smoking cessation therapies is readily apparent.

Indeed, the need for innovation in smoking cessation drugs was recognized by Congress when it amended the Food, Drug and Cosmetic Act in 2009 by enacting the Family Smoking Prevention and Tobacco Control Act (TCA). In the TCA, Congress declared that a purpose of the new law was "to promote cessation to reduce disease risk." TCA §3(a). To that end, Congress enacted section 918 of the FDCA, which specifically directed FDA to look for ways to expand the reach of NRTs. Under section 918, FDA must:

> (1) at the request of the applicant, consider designating products for smoking cessation, including nicotine replacement products, as fast track research and approval products within the meaning of section 506;

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[4] See generally, *HHS Framework to Support and Accelerate Smoking Cessation 2024,* at 2-3 (HHS Framework).
[5] Cunningham, PJ, "Why Even Healthy Low-Income People Have Greater Health Risks Than Higher-Income People," The Commonwealth Fund, 27 Sept. 2018, https://www.commonwealthfund.org/blog/2018/healthy-low-income-people-greater-health-risks;
[6] HHS Framework, at 8.
[7] HHS, Office of the Surgeon General, "Smoking Cessation: A Report of the Surgeon General," 2020 https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-report.pdf.
[8] VanFrank B, Malarcher A, Cornelius ME, Schecter A, Jamal A, Tynan M. Adult Smoking Cessation — United States, 2022. MMWR Morb Mortal Wkly Rep 2024;73:633–641. DOI: http://dx.doi.org/10.15585/mmwr.mm7329a1. (VanFrank et al.)
[9] Siu, AL, "Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement," *Annals of Internal Medicine* 163(8):622-34, October 20, 2015. Cahill, K, et al., "Pharmacological interventions for smoking cessation: an overview and network meta-analysis," *Cochrane Database of Systematic Reviews* 4:CD009329, 2013.
[10] VanFrank et al.
[11] Siu, AL, "Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement," *Annals of Internal Medicine* 163(8):622-34, October 20, 2015. Fiore, MC, et al, *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*, Rockville, MD: HHS, May 2008.
[12] HHS Framework, at 2.
[13] HHS, *Report to Congress: Innovative Products and Treatments to Achieve Abstinence from Tobacco Use, Reductions in Consumption of Tobacco, and Reductions in the Harm Associated with Continued Tobacco Use*, Required by Section 918 of the FDCA, April 22, 2013.

> (2) consider approving the extended use of nicotine replacement products (such as nicotine patches, nicotine gum, and nicotine lozenges) for the treatment of tobacco dependence; and
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> (3) review and consider the evidence for additional indications for nicotine replacement products, such as for craving relief or relapse prevention.

21 U.S.C. 387r(a). Twenty-five years after enactment of the TCA, there has been little progress in the development and marketing of effective smoking cessation therapies. The need for change has never been clearer.

For years, the public health community has expressed concern about restrictions placed on the labeling and use of existing smoking cessation products, as well as the structural and regulatory barriers that may discourage the development of new, more effective drugs. FDA itself has underscored the need to reassess the agency's approach to smoking cessation therapies as well. In his July 2017 announcement of a new comprehensive approach to nicotine and tobacco, then-FDA Commissioner Scott Gottlieb stated that "we must also work to have medicinal nicotine and other therapeutic products play a greater role in helping more smokers try to quit with help, to quit successfully, and to stay quit." He called on FDA's Center for Drug Evaluation and Research (CDER) "to examine possible steps we can take to address the performance of medicinal nicotine products" and "other possible innovations in treatments that could help more smokers use FDA-approved products to quit smoking."[14] Although Commissioner Gottlieb created a cross-agency Nicotine Steering Committee, which was "charged with re-evaluating and modernizing FDA's approach to the development and regulation of nicotine replacement therapy products that help smokers quit,"[15] no significant reforms emerged from that initiative. More recently, prior to convening the public meeting, leaders from FDA and NIH recognized the "urgent need for continued development of highly efficacious treatments for smoking cessation."[16] Thus, we reiterate our call for FDA, in its consideration of current and future therapeutic treatments for smoking cessation, to recognize the need for a new regulatory environment that will eliminate arbitrary regulatory barriers to the widespread and effective use of approved smoking cessation drugs and encourage responsible companies to develop innovative new cessation drugs that are safe and effective.

The urgent need for new, innovative products that are proven safe and effective for smoking cessation is underscored by the emergence of e-cigarettes and related products. These highly addictive nicotine products have been marketed to young people for recreational purposes, leading to persistently high rates of youth usage. Millions of smokers are using e-cigarettes to help them stop smoking, even though no application for new drug approval has even been submitted to FDA by an e-cigarette manufacturer.[17] Yet, as discussed above, the current FDA-approved medications are not widely used, a factor that has likely contributed to e-cigarette makers' efforts to fill the void and consumers' willingness to look to e-cigarettes as a smoking cessation aid, even though they are an unproven alternative.

Unfortunately, current FDA regulation of nicotine products has created a perverse incentive structure: it rewards companies that market e-cigarettes to as many consumers as possible for recreational use, including young people, while creating substantial disincentives—like high costs and prohibitive delays—for companies to pursue CDER approval of drugs backed by sound science establishing that their products are safe and effective at helping smokers quit.

FDA should correct this current imbalance through a coordinated agency-wide effort that must include a careful assessment of the barriers faced by responsible companies who wish to pursue the CDER pathway to market. FDA need not wait for product manufacturers to submit NDAs or supplemental NDAs for particular products, but should proactively

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[14] "Protecting American Families: Comprehensive Approach to Nicotine and Tobacco," Remarks by Scott Gottlieb, M.D., Commissioner of FDA, July 28, 2017. https://www.fda.gov/news-events/speeches-fda-officials/protecting-american-families-comprehensive-approach-nicotine-and-tobacco-06282017

[15] Scott Gottlieb, M.D., Janet Woodcock M.D., Mitchell Zeller, JD, "Advancing Medicinal Nicotine Replacement Therapies as New Drugs – A new step in FDA's comprehensive approach to tobacco and nicotine," FDA Voice, November 29, 2017. https://www.fda.gov/news-events/fda-voices/advancing-medicinal-nicotine-replacement-therapies-new-drugs-new-step-fdas-comprehensive-approach

[16] H.J. Warraich, MD, et al., "Opportunities for Innovation in Smoking Cessation Therapies: A Perspective from the National Institutes of Health and U.S. Food and Drug Administration," *Annals of Internal Medicine* (Oct. 15, 2024), at 1. (Warraich, et al.) https://www.acpjournals.org/doi/10.7326/ANNALS-24-02318

[17] Warraich et al., at 3.

establish policies and processes based on the available evidence to maximize the public health impact of existing products and create a new environment for innovation for smoking cessation products. In addition, CTP must do its part by continuing to deny marketing authorization for flavored e-cigarette products and by aggressively enforcing the law against all unauthorized e-cigarettes that continue to be sold.[18]

We offer the following concrete suggestions for a new approach to the approval of smoking cessation therapies.

II. IN WEIGHING THE RISKS OF SMOKING CESSATION PRODUCTS, FDA SHOULD IDENTIFY CONTINUED SMOKING AS THE RELEVANT COMPARATOR

Cigarettes kill half of their long-term users[19] and millions of smokers suffer from debilitating smoking-related diseases. Thus, when assessing the risks of new indications or labeling changes for existing approved products, or the safety of new products, FDA must compare the risks posed by the cessation therapy to the risk posed by continued smoking. Although CDER has recognized "tobacco dependence to be a serious or life-threatening condition,"[20] there is little evidence that it uses continued smoking as the relevant comparator in its risk/benefit assessments of cessation products.

Evaluating a product in this way does not require CDER to compromise its safety standards at all. Rather, it ensures appropriate consideration of the ultimate risks from continued smoking. FDA regularly assesses product safety and risk in the full context of the condition for which the product is used. As one example, certain cancer therapies may themselves be toxic or cause serious side effects, yet have been found to be important treatments for patients suffering from debilitating cancers. Not only must FDA use continued smoking as the relevant comparator, it should also make it clear to the pharmaceutical industry, and the public, that it will do so in assessing the risks posed by smoking cessation products that are the subject of NDAs submitted to CDER.

III. FDA SHOULD TAKE PROACTIVE STEPS TO DEMONSTRATE ITS WILLINGNESS TO CONSIDER NEW INDICATIONS AND LABELING CHANGES FOR EXISTING SMOKING CESSATION PRODUCTS

The existing body of scientific knowledge supports cessation treatment regimens that are safe and effective (particularly if continued smoking is genuinely weighed in the benefit/risk analysis), but that are not reflected in the current labeling of NRTs and other cessation products currently on the market. Strong, well-documented, peer-reviewed evidence exists to support the following changes in labeling and indications:

Combination use. The U.S. Public Health Service Clinical Practice Guidelines found strong scientific evidence that some smokers derive substantial benefit from the combination use of a nicotine patch and a more rapid-delivery form of NRT, such as gum or spray, as compared to use of one NRT alone.[21] CDER's 2023 NRT Guidance makes reference to a potential new treatment regimen of using two NRT drug products together, but nothing in the current labeling of NRTs communicates the effectiveness of certain combinations of NRTs.

Longer-term use of NRTs. None of the FDA-approved NRT products is approved for long-term use, i.e., use beyond the 12-week schedule in the current labeling. However, many smokers who try to quit are unable to do so within the length of time approved for smoking cessation products. According to the PHS Clinical Practice Guidelines, long-term NRT use is safe and effective for smoking cessation. It is encouraging that the 2023 NRT Guidance suggests that, under certain circumstances, approval of longer-term use may require only a single adequate and well-controlled efficacy

[18] *See generally*, Letter from 78 public health, medical and other organizations re need for stronger enforcement against unauthorized e-cigarettes (May 22, 2024). https://assets.tobaccofreekids.org/content/press_office/2024/2024_05_22_coalition-letter-e-cig-enforcement.pdf

[19] 2014 SG Report.

[20] Center for Drug Evaluatioin and Research, FDA, *Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products, Guidance for Industry* (May 2023), at 4. (2023 NRT Guidance).

[21] Fiore, MC, et al., *Treating Tobacco Use and Dependence: 2008 Update,* U.S. Public Health Service Clinical Practice Guidelines, May 2008 (PHS Clinical Practice Guidelines).

trial and appropriate PK bridging studies.[22] Nevertheless, the current labeling of NRTs fails to indicate that long-term use of NRTs may be effective.

Pre-quit NRT use in "reduce to quit" regimen. At its 2018 hearing, the Nicotine Steering Committee heard testimony that a "reduce to quit" regimen with NRT is more effective than placebo and results in quit rates comparable to abrupt cessation.[23] The 2023 NRT Guidance suggests that, under certain circumstances, approval of a treatment regimen involving quitting by gradual reduction may require only a single adequate and well-controlled efficacy trial and appropriate PK bridging studies.[24] Yet nothing in the current labeling of NRTs indicates the effectiveness of a properly conducted reduce to quit strategy.

Labeling changes to better communicate that NRTs are much safer than continued smoking. At its 2018 hearing, the Nicotine Steering Committee heard testimony that existing warning labels discourage the use of NRTs because the warnings do not sufficiently communicate that NRTs are substantially less harmful to health than continued cigarette smoking. Studies reveal significant misperceptions or lack of knowledge, among smokers and healthcare providers, about the harm of nicotine and NRTs.[25] Warnings could be revised to provide smokers with well-established facts about the dangers of smoking compared to the comparatively low risks of side effects from NRTs.

In short, powerful scientific evidence supports new uses of existing approved products. Nevertheless, insufficient progress has been made toward making the necessary labeling changes that will encourage more frequent and effective uses of approved NRTs.

IV. FDA SHOULD EXPLORE ALTERNATIVES TO LONG-TERM CLINICAL TRIALS FOR PROMISING NEW PRODUCTS OR FOR NEW INDICATIONS FOR EXISTING PRODUCTS

For particularly promising new products and indications, and without weakening the standards for safety and effectiveness, FDA can broaden the kind and scope of scientific evidence that may support claims of safety and effectiveness beyond long-term clinical trials. There is a wealth of data about the effects of nicotine delivery, both from decades of use in the U.S as well as from the widespread use of nicotine delivery products in various forms all over the globe. FDA should create a docket to solicit the best available scientific evidence, including convening leading experts, to determine whether there is sufficient support for the use of alternative data and methods to assess safety and effectiveness for cessation products that would allow for shorter-term and less expensive clinical trials. This could include the use of existing clinical data, epidemiological data, and other real-world data without compromising FDA's safety and efficacy standards.

Based upon the existing global experience with products that deliver nicotine and the peer review published literature, we believe evidence criteria can be developed that reduces costs and expedites the review process without compromising or creating an exception to FDA's existing standards.

V. FDA SHOULD ESTABLISH CRITERIA FOR THE USE OF ACCELERATED PATHWAYS FOR PROMISING SMOKING CESSATION DRUGS

One of the barriers to innovation in smoking cessation products is the amount of time required to pursue NDAs or SNDAs. That problem has become even more consequential in light of the fast-changing nature of the nicotine product market in the past few years. Given the continuing population-wide harms of smoking and the relative paucity of effective, widely used therapeutic treatments, smoking cessation products should be leading candidates for accelerated approval and priority review. Indeed, Congress agreed: as noted above, in the Tobacco Control Act, Congress directed FDA to consider treating cessation products as fast track research and approval products at an applicant's request. *See* 21 U.S.C. 387r(a)(1). The 2023 NRT Guidance made it clear that "FDA considers tobacco dependence to be a serious or life-threatening condition," meriting case-by-case consideration of "whether an NRT drug product meets the criteria (e.g. significant improvement over existing therapies, address an unmet medical need) for inclusion in FDA's expedited

[22] 2023 NRT Guidance, at 7.
[23] Dr. Dorothy Hatsukami, Comments on Nicotine Replacement Therapies from the American Association for Cancer Research (January 26, 2018) Slide #11 (Hatsukami).
[24] 2023 NRT Guidance, at 7.
[25] Hatsukami, Slide #12.

development and review pathways."[26] FDA should also make it clear that such accelerated pathways may be available for promising cessation drugs other than NRTs.

While FDA acknowledged the potential applicability of accelerated pathways to cessation therapies in the 2023 NRT Guidance, FDA should provide potential product sponsors with additional details of the standards that would apply and benefits that would accompany such priority treatment. FDA can do so by collecting the best available evidence, setting forth clear, specific criteria for eligibility of specified types of products for fast track treatment and/or as breakthrough therapies, and clearly delineating the showing needed for a smoking cessation product to receive such treatment.

VI. FDA SHOULD ENCOURAGE THE DEVELOPMENT OF CESSATION THERAPIES IN PEDIATRIC POPULATIONS

As FDA acknowledges, 90 percent of adult daily smokers started smoking before they turned 18. This fact makes it essential to ensure that tobacco cessation products are effective for and available to the adolescent population. Unfortunately, however, there is a significant gap in the availability of cessation products with labeling for use in pediatric populations. FDA should encourage sponsors of tobacco cessation products to develop them for, and study them in, pediatric populations.

Research to date has shown that NRTs have different effects on adolescents compared to adults. It is therefore imperative that sponsors, when appropriate, develop pediatric plans as early as possible in the drug development process so that well-constructed research is conducted in adolescents and that adolescent needs are taken into account when designing product characteristics.

The widespread use of e-cigarettes by youth has created new urgency for the development of drug therapies that can treat nicotine addiction among the young. E-cigarettes have been the most popular tobacco product among youth since 2014, with youth usage rising to epidemic proportions during the 2018-20 period. Youth e-cigarette use remains unacceptably high today, with 1.6 million high school and middle school students currently using these products.[27] Although the prevalence of youth e-cigarette use has declined in recent years, frequent and daily use among youth users has remained at high levels. In 2024, 42.1% of high school e-cigarette users reported using e-cigarettes on at least 20 of the past 30 days, and 29.7% reported *daily* use.[28] These data indicate high levels of addiction among youth e-cigarette users. There is an urgent need for research to better understand nicotine addiction among adolescents generally, but particularly nicotine addiction from e-cigarette use.

Respectfully submitted,

Campaign for Tobacco-Free Kids

[26] 2023 NRT Guidance, at 4. See also, Warraich, et al., at 3.
[27] Eunice Park-Lee et al. Notes from the Field: *E-Cigarette and Nicotine Pouch Use Among Middle and High School Students*, 73 MORBIDITY & MORTALITY WKLY. REP. 774, 774 (2024), https://www.cdc.gov/mmwr/volumes/73/wr/pdfs/mm7335a3-H.pdf.
[28] Park-Lee et al., at 775 tbl.