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Food and Drug Administration
Center for Tobacco Products
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Docket No. FDA-2024-N-5471, "**Tobacco Product Standard for Nicotine Yield of Cigarettes and Certain Other Combusted Tobacco Products**"

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the world's first and largest scientific organization dedicated to cancer research, we express our sincere appreciation for the opportunity to provide the U.S. Food and Drug Administration (FDA) with information from our Tobacco Products and Cancer Subcommittee, a group of experts on topics including nicotine addiction, smoking cessation, and lung cancer, regarding the proposed tobacco product standard to establish a maximum nicotine level in cigarettes and certain other combusted tobacco products. We recognize the significant impact any comments may have on future regulation in this space, and we commend the agency's commitment to listening to patient, researcher, and clinician voices.

The pharmacology of nicotine sustains the use of and dependence on tobacco products. Among tobacco products, cigarettes and other combustible products confer the most significant harms to users. Tobacco use has been associated with 18 types of cancer and is the leading cause of premature cancer deaths in the United States (1,2). Cigarette smoking is associated with cardiovascular, metabolic and respiratory diseases and is the overall leading cause of preventable deaths in the United States. Reducing nicotine content in cigarettes and other combustible products to minimally or non-addictive levels would significantly reduce smoking, and subsequently, many cancers, chronic diseases, and overall tobacco-caused deaths.

The Family Smoking Prevention and Tobacco Control Act authorizes FDA to set standards on tobacco product characteristics, including their appeal, toxicity, and addictiveness, if the standard is appropriate for public health and does not reduce nicotine content to zero. FDA has been collecting and generating gold-standard supporting research to determine the utility of a nicotine product standard (NPS) for at least a decade. It is clear that the proposed rule meets the criteria for being appropriate for the protection of public health, as FDA itself reports that implementing this policy would prevent approximately 48 million American youths and young adults from initiating smoking by 2100, lead to nearly 20 million Americans quitting smoking within five years of implementation, and provide $1.1 trillion in financial benefits each year over the first four decades of implementation (3,4). The NPS is a scientifically driven, feasible, and common-sense approach to reducing death and disease in this country, and if implemented would be among the most impactful cancer prevention and anti-chronic disease polices in American history.

AACR is publishing a forthcoming article, titled "An AACR Policy Statement to Support a Federal Limit on Nicotine in Combustible Tobacco and Protect Public Health" in the peer-reviewed journal *Clinical Cancer Research*. This article, as well as this comment, express AACR's fervent support for the NPS, highlight major scientific findings and clinical trials informing the NPS, and outline

accompanying considerations that would further increase the positive impact of the proposed NPS on the health of all Americans.

Evidence to Support a Nicotine Product Standard

Several comprehensive reviews have been conducted on studies simulating an NPS (4–9). Cumulatively, these randomized clinical trials have involved thousands of people who smoke (PWS) and have consistently shown reductions in smoking-related behaviors mediated by switching to very low nicotine cigarettes (VLNCs), resulting in less exposure to carcinogens and increases in quit attempts and smoking cessation (5–24). In general, these results hold without regard for gender, or race/ethnicity, educational attainment levels, or socioeconomic class. Other populations of interest, including youth and young adults who smoke, PWS with comorbid medical and psychiatric conditions, people with depression, and those who use alcohol, cannabis, or menthol cigarettes also experienced substantial benefits.

While the 0.7 milligrams per gram (mg/g) nicotine concentration cap proposed in the NPS is slightly higher than the 0.4 mg/g VLNC dose reported to be used in many studies simulating an NPS, it also represents an approximately 95 percent reduction in concentration for the majority of modern American combusted cigarettes. FDA reports that some cigarettes used in clinical trials as VLNCs with 0.4mg/g nicotine may have varied between 0.4 mg/g to 0.7 mg/g (25). Taking this information together, the scientific literature generally supports the proposed maximum nicotine level of 0.7 mg/g. AACR recommends that FDA does not increase this proposed maximum further.

Additionally, research has shown that reducing nicotine levels immediately, rather than gradually, would provide the greatest public health benefit while also being the simplest approach. Using a stepwise reduction approach significantly increases complexity by requiring multiple changes in manufacturing processes and differing enforcement across time (26). Additionally, stepwise approaches have been shown to be less effective at producing cessation, with PWS assigned to gradual reduction being significantly less likely to quit smoking than those assigned to switch to VLNC immediately. Those who were assigned to gradual reductions also displayed increased smoking intensity, indicative of attempts to compensate for decreasing nicotine levels, whereas those assigned to VLNC immediately did not (10). Based on these results and the practicality of implementation, AACR recommends that FDA continues to support a single date whereby all products included in the NPS must decrease to 0.7 mg/g nicotine.

It is unlikely that implementing the NPS will lead to negative unintended consequences. On a person-level, there may be concerns regarding withdrawal symptoms, exacerbation of existing mental health conditions, increased compensatory smoking, the potential for switching to other combusted products, increased experimentation by youth, and a feeling of reduced choice on the part of PWS. While some studies indicate that PWS assigned to VLNC experience withdrawal symptoms, other studies indicate withdrawal symptoms are not significant when switching to VLNC (6,9,10,27,28). No increases in alcohol consumption or cannabis use have been seen in PWS assigned to VLNCs, with the exception of very slight increases among those who already use cannabis (20,21,29–31). Additionally, no increases in psychiatric symptoms has been observed in PWS assigned to VLNC who are diagnosed with serious mental illness, and greater

improvements in depressive symptoms have been seen in those randomized to VLNC as compared to NNC (19,22). Signs of significant compensatory smoking have not been observed, with VLNC cigarettes leading to decreases in cigarette consumption and biomarkers of smoke exposure (9,17,32,33). These results indicate a lack of negative personal effects on people who switch. However, PWS assigned to VLNC have been shown to use alternative combusted tobacco products when given access (34); this is why it is imperative that a finalized NPS include all cigarette-like and other combusted products currently included in the proposed rule. This would instead encourage the use of medicinal nicotine replacements or other alternative products less harmful than combustibles, which would also serve to decrease any potential withdrawal symptoms. Additionally, because VLNCs cannot sustain addiction, it is unlikely that anyone experimenting with them would exhibit continued use since they are unrewarding. Finally, implementation of the NPS will increase freedom, not lower it, for the almost 70% of PWS who want to quit and 90% of those who want to quit that are unsuccessful (35). Reducing the addictiveness of cigarettes would ease the actualization of an individual's choice to continue or stop smoking. It is highly likely that any unintended consequences will be outweighed by the massive public health benefits provided by the NPS.

Additional Considerations for Implementing a Nicotine Product Standard

Multiple studies conducted by FDA scientists have estimated the impacts of an NPS. As stated previously, the most recent update to the FDA model shows that if NPS enforcement began in 2027, 12.9 million additional PWS would quit smoking within the first year, 19.5 million PWS would quit within five years, and 1.8 and 4.3 million deaths would be avoided by 2060 and 2100 respectively (3,4). These gains could be further maximized if FDA collaborated with other federal agencies on supporting policies.

Numerous clinical trials have shown that nicotine replacement therapy, varenicline, bupropion, and counseling increase participants' odds of short- and long-term abstinence from nicotine (36–38). Several trials have found that combining FDA-approved nicotine replacement therapy with the use of VLNC cigarettes may improve smoking-related outcomes compared to VLNC cigarettes alone (12,39). Ensuring access and insurance coverage for such evidence-based cessation therapies for PWS would elevate the public health benefits of the proposed NPS.

Some have raised concerns that the implementation of the NPS would increase the size of the illicit cigarette marketplace. However, alternative products with nicotine content higher than that of very low nicotine cigarettes will remain available, cutting potential demand, and any operations with a large enough scale to limit the benefits of the NPS would be impossible to hide from law enforcement. To alleviate all concerns regarding the unlikely development of a significant illegal marketplace, a strong track and trace system with sufficient enforcement capabilities and penalties to the manufacturers, distributors, retailers, and importers should accompany the NPS.

Evidence-based services such as SmokeFree.gov and the National Quitline (1-800-QUIT-NOW) are free and powerful resources that support smoking cessation. Continued funding for federal tobacco control programs that support state and national quitlines will be essential to help as many people quit smoking as possible upon NPS implementation.

While an NPS has been shown to help people across populations quit smoking, certain populations have been shown to experience less benefit than others. For example, PWS who self-report being African American or smoke menthol cigarettes experienced less of a reduction in cigarette smoking when randomized to VLNCs as compared to those who are White or who smoke non-menthol cigarettes, respectively (16,40). Potential action that could amplify and equalize the benefits seen across populations include re-introducing and finalizing the previously proposed standard calling for the removal of menthol from combusted tobacco products, including for VLNC products.

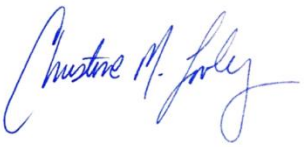
Significant misperceptions remain among the public regarding the relative harms of tobacco products, such as the idea that e-cigarettes are just as harmful as cigarettes (41). Educating adult PWS about the continuum of risk, in accordance with recent similar FDA messaging, while maintaining reduced uptake among youth and non-users is essential (42). Making sure these messaging efforts reach all Americans regardless of background will also help equalize any discrepancies in benefit experienced by specific populations. Increasing educational efforts regarding the harms of tobacco use and the continuum of risk of tobacco products would help maximize the benefits of the NPS.

Summary

Limiting nicotine levels in cigarettes and other selected combusted tobacco to minimally or non-addictive levels as proposed in the NPS would have profound positive public health impacts. Finalization of the NPS is supported by numerous randomized clinical trials and represents a feasible common-sense approach to powerfully reducing cancer, chronic disease, and death in America. Specifically, a broad and convergent set of studies support the nicotine level selected, the use of immediate reduction, and show that it is unlikely that any unintended consequences could come close to outweighing the massive public health benefits that would be conferred by the NPS. A comprehensive NPS implementation strategy, including increased education, access to cessation tools, and federal support for tobacco control programs, as well as established track and trace systems and the re-introduction of the previously proposed menthol product standard would maximize the public health benefits and mitigate any such unintended consequences.

We strongly encourage the FDA to finalize this comprehensive rule for the betterment of all Americans.

Sincerely,



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