June 12, 2018

Gerie Voss
Center for Tobacco Products
Food and Drug Administration
10903 New Hampshire Avenue
Building 71, Room G335
Silver Spring, MD 20993

Re: Docket No. FDA-2017-N-6189 for Tobacco Product Standard for Nicotine Level of Certain Tobacco Products.

Dear Ms. Voss:

We, the Presidents of the American Psychological Association, the College on Problems of Drug Dependence, and the Society for Research on Nicotine and Tobacco, are writing representing the principal organizations dedicated to the advancement, understanding, and dissemination of research on the behavioral and psychological sciences, substance use and dependence, and nicotine and tobacco, respectively. Collectively, we represent thousands of scientists working on all aspects of drug dependence and addiction, from molecular neuroscience and gene expression to social and cultural determinants of substance use behavior.

We appreciate the opportunity to comment on the Advance Notice of Proposed Rulemaking as the Food and Drug Administration (FDA) considers developing a tobacco product standard to set the maximum nicotine level for cigarettes. Our comments are organized as a series of key points derived from the scientific literature that we hope will provide useful guidance to FDA as it pursues this critically important public health objective:

Key Point 1: *Addictive agen*t. Nicotine is the primary addictive agent in tobacco products.[1-3] Other constituents such as minor alkaloids, norharmae, and aldehydes may contribute to the addictiveness of tobacco products[4-6] but at doses that are higher than found in cigarettes.[7] MAO inhibitors may increase the self-administration of low doses of nicotine in rats, but have minimal effects at very low doses.[8] To the best of our knowledge, no studies have been conducted in humans to suggest that these constituents alone would sustain tobacco use or augment the effects of nicotine. That being said, tobacco product testing that would ensure that tobacco products are not being manufactured to enhance the addictiveness in reduced nicotine cigarette (e.g., adding nicotine analogues) would be important. Product standards that would not allow the

levels of these constituents to be above what is found in currently marketed conventional cigarettes would also be advised.

Key Point 2: ***Threshold dose of nicotine*****.** Based on the findings from larger clinical trials, the minimally addictive level is likely to be less than or equal to 0.4 mg nicotine/gram of tobacco. At this dose, relative to normal nicotine content cigarettes (15.8 mg nicotine/gram of tobacco), significant decreases were observed in cigarettes smoked and dependence. Additionally, a higher proportion of smokers made a quit attempt.[9] This dose was also associated with significantly reduced biomarkers of exposure to tobacco specific nitrosamines, polycyclic aromatic hydrocarbons and volatile organic compounds.[10] Furthermore, the number and type of serious and severe adverse events were found to be similar across normal and reduced nicotine doses.[10]

Key Point 3: ***Vulnerable populations*****.** It is important to set any product standards at levels that will be sufficiently protective of vulnerable populations. The 0.4 mg nicotine/gram tobacco dose has been observed to consistently be less reinforcing than the 15.8 mg nicotine/gram tobacco dose in a population of smokers who have co-morbid substance use and affective disorders and who are of lower socioeconomic status.[11] Furthermore, among smokers with elevated depressive symptom scores at baseline, lower nicotine content cigarettes led to reduced cigarette smoking and dependence, without worsening depressive symptoms.[12] Smokers with a history of cannabis[13] or alcohol[14] use experienced similar reductions in smoking and dependence with reduced nicotine cigarettes as compared to smokers without these histories, and reported no increase in alcohol and cannabis use. Further research on the behavioral effects of longer-term use of reduced nicotine content cigarettes among those smokers with co-morbid disorders is currently underway.

Younger adults (ages 18-24 years) who were assigned cigarettes from 2.4 to 0.4 mg nicotine per gram tobacco initially reported lower positive cigarette effects than smokers aged 25 and older, but the differences diminished after two weeks of use, suggesting that older adults began to experience less reinforcing effects after a period of use.[15] A laboratory study with youth showed that lower doses of nicotine were associated with less satisfaction and psychological reward than higher doses of nicotine.[16] Results from longer term use of very low nicotine content cigarettes in the natural environment among youth will be forthcoming. Because a few studies have shown greater sensitivity to the reinforcing effects of nicotine in adolescent compared to adult rats,[17,18] lower doses of nicotine as a product standard should be considered.

Key Point 4: ***Compensatory smoking*****.** Unlike cigarettes that were formerly called "light" or "ultralight" for which nicotine yields were reduced due to cigarette design features (such as perforations in cigarette filter) rather than reductions in nicotine levels in the tobacco filler, very low nicotine content cigarettes have reduced nicotine content in the tobacco itself. As a result, the majority of studies have shown minimal compensatory smoking with very low nicotine content cigarettes (0.4 mg/g tobacco or Quest 1 at 0.05 mg machine determined nicotine yield).[19-22]

Key Point 5: ***Stepped down or immediate nicotine reduction*****.** Immediate nicotine reduction is likely to have the largest public health benefit. However, a gradual or stepped down approach to reducing nicotine in cigarettes may lead to less severe withdrawal symptoms, fewer number of people experiencing withdrawal, and may be more acceptable to cigarette smokers. However, studies suggest that compensatory smoking may occur at moderate doses of reduced nicotine content cigarettes.[10,20-23] Furthermore, gradual nicotine reduction would lead to more sustained use of the cigarettes and prolonged exposure to tobacco toxicants [10], and potentially continued youth progression to dependence during minimal to moderate dose reductions.

Key Point 6: ***Alternative sources of nicotine*****.** Regardless of the approach to reducing nicotine content in cigarettes, some percentage of smokers are likely to seek other sources of nicotine. Prior experimental studies showed that a significant number of smokers "cheat" by smoking non-study, conventional nicotine level cigarettes[9,23-25] or when provided the opportunity, seek other sources of nicotine.[26] These sources may include medicinal products that would alleviate withdrawal symptoms[24,27] and may help smokers quit smoking, or alternative sources of nicotine such as electronic nicotine delivery systems.[26] If a product standard for reducing nicotine in cigarettes is implemented, every effort should be made to facilitate smoking cessation. Alternately, smokers who cannot or do not want to quit using nicotine should be transitioned from combusted products to less harmful nicotine-containing products, including medicinal nicotine. These efforts could entail educating smokers about the relative harms of various tobacco products and medicinal nicotine, and ensuring that these alternative nicotine products are appealing and have sufficient amounts of nicotine so that the transition is not difficult.

Key Point 7: ***Scope of regulation*****.** At minimum, the FDA should expand the reduction of nicotine in cigarettes to high toxicity combusted products that could be used as cigarette substitutes. These include little cigars, cigarillos and roll your own tobacco. Although studies have shown greater abuse liability of conventional cigarettes compared to little cigars,[28] large cigars,[28] and loose smoking tobacco,[28,29] if cigarettes are reduced in nicotine content, inhaled tobacco products with similar pH are likely to be substituted for cigarettes.[28-31] The FDA should also consider other highly toxic products, such as premium cigars, pipe tobacco, and hookah for nicotine reduction, though additional studies may be needed to determine how these products will act as substitutes for reduced nicotine content cigarettes. In general, the criteria to consider in evaluating whether or not to reduce the addictiveness of other combusted products include the abuse liability, toxicity, and patterns of use (e.g., frequency and amount of use).

Key Point 8: ***Illicit market.*** Modeling the potential beneficial public health effects of reducing nicotine content in cigarettes has been demonstrated to be significant (8.5 million tobacco caused deaths averted by 2100 and the prevalence of smoking reduced to 1.4%[32]). The authors of this modeling study referred to the 2015 IOM report on *U.S. Illicit Tobacco Market*,[33] which stated that demand for illicit conventional cigarettes resulting from their modification in the licit market may be modest. This was the case in earlier public health impact analyses by Teng et al.,[34] who projected the prevalence of smoking to decrease to 5% even when accounting for a 10% increase in black market

cigarette purchases. Ensuring that an infrastructure and rapid methods of assessments are in place to monitor, test, and enforce penalties on illegal trade is likely to limit the effects of the illicit market on the public health benefits of the nicotine reduction policy.

Key Point 9: ***Communication about the harms of nicotine.*** Education is needed to correct the misperceptions of nicotine's harm among the public as well as health professionals. Studies have demonstrated that in a significant number of individuals, nicotine is perceived as one of the toxic chemicals in tobacco products that causes cancer.[35-40] This misperception has led to the belief that reduced nicotine cigarettes are less harmful than cigarettes that contain normal amounts of nicotine.[41-43] It is important to convey the message that these cigarettes are just as harmful as cigarettes with higher levels of nicotine, but they may help people quit smoking, and keep people from being addicted to smoking, because of their reduced addictiveness. This misperception of nicotine has led smokers to even be concerned about the use of medicinal nicotine products. For a reduced nicotine policy to be maximally effective, communication efforts need to correct misperceptions about nicotine, prevent initiation, and promote smoking cessation to minimize potential individual-level and population-level harms.

Key Point 10: ***Communication of regulatory approach*****.** A high percent of smokers and non-smokers support a regulation to reduce nicotine in cigarettes in the general population[44] and even among those who have experienced use of very low nicotine content cigarettes (Eric Donny, personal communication; Dorothy Hatsukami personal communication). Communicating the rationale for this regulatory approach and ways to prepare for it will maximize potential benefits.

Key Point 11: ***Making cessation available*****.** Reducing nicotine in cigarettes is likely to lead to a significant number who are seeking to quit cigarette smoking. In Donny et al., 2015,[9] about 1/3 of the population of smokers uninterested in quitting made a quit attempt. As a result, systems-level and provider-level interventions are needed to ensure that the most effective smoking cessation support is accessible and affordable.

Key Point 12: ***Generalizability of results*****.** Although several studies have been conducted to examine the effects of reducing nicotine in cigarettes, most of these studies are conducted using controlled experimental designs. The inclusion criteria are stringent, cigarettes are provided for free and in almost all studies, smokers are told not to use any other sources of nicotine besides study cigarettes. To date, more naturalistic studies or community-wide studies have not been conducted to determine the real individual and societal impact of reducing nicotine in cigarettes. Although the potential societal impact has not been quantified, the evidence to-date supports that a reduced nicotine content standard for combusted cigarettes would benefit public health. Therefore, if the regulation is implemented, then it would be important to have ongoing surveillance and continued research to maximize public health benefits and minimize unintended consequences.

Key Point 13: ***Comprehensive tobacco control efforts*****.** A regulatory approach to reduce nicotine in cigarettes should not detract from evidence-based tobacco control programs

such as increasing the price of cigarettes, smoking prevention and cessation media campaigns, comprehensive smoke-free laws, and making effective smoking cessation treatments accessible and affordable to smokers, or any prevention efforts such as increasing the legal age for purchase of cigarettes to age 21.

In summary, there is a growing number of studies that demonstrate the promise of reducing nicotine in cigarettes. The Society for Research on Nicotine and Tobacco, the College on Problems of Drug Dependence, and the American Psychological Association are very interested in engaging and collaborating with the Food and Drug Administration to address remaining research questions and to ensure that any resulting regulation reflects the best available science. We are research organizations that are invested in reducing the burden of tobacco use and in providing the scientific basis for achieving this goal.

Sincerely,

Jessica Henderson Daniel, PhD, ABPP
President, American Psychological Association

Alan J. Budney, PhD
President, College on Problems of Drug Dependence

Marina Picciotto, PhD
President, Society for Research on Nicotine and Tobacco

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