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Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Tobacco Product Standard for Nicotine Level of Combustible Cigarettes (FDA-2017-N-6189-0001)

Commissioner Gottlieb:

On behalf of the 16,000 members of the American Thoracic Society (ATS), I want to thank FDA for the opportunity to comment on the Advanced Notice of Proposal Rule Making (ANPRM) regarding Tobacco Product Standard for Nicotine Level of Combustible Cigarettes. (docket number FDA-2017-N-6189-0001). As chair of the ATS Tobacco Action Committee, I appreciate the opportunity to comment on this important public health issue.

As background, the ATS is comprised of over 16,000 physicians, scientists, nurses, respiratory therapists and allied health professionals dedicated to the prevention, detection, treatment, and cure of pulmonary disease, critical care illness and sleep disordered breathing. Our members seek to improve health through research, education, clinical care and advocacy. As respiratory experts, our members are all too familiar with the disease, death and emotional destruction caused by tobacco products, including cigars. Many of our members have made seminal contributions to the evidence foundation for tobacco control. As researchers, we are well aware of the extensive scientific evidence base that documents the known adverse health effects of tobacco products and secondhand tobacco smoke. It is with this expertise and organizational commitment to tobacco control that the ATS offers the following comments:

FDA's Comprehensive Plan for Tobacco and Nicotine Regulation
The ATS has reviewed with great interest FDA's comprehensive plan for tobacco and nicotine regulation, as announced in 2017 and further detailed in the ANPRM.

Based upon our careful reading of materials describing the comprehensive plan, our review of the ANPRM, and FDA's other regulatory actions, it is clear that the agency is formulating policies that, over time, are intended to shift tobacco use patterns from combustible cigarettes to non-combustible nicotine products, namely e-cigarettes and future generations of such products. While not explicitly stated in the comprehensive plan, the agency appears to be committed to a "harm reduction" approach to reducing the disease burden of tobacco use, moving smokers of combustible cigarettes, at least those unable to quit, towards less risky nicotine-delivering products.

The ATS recognizes the hypothetical benefits of a harm reduction strategy around combustible cigarettes. As noted in FDA's ANPRM, any action that will reduce the appeal and addictiveness of cigarettes will likely yield significant public health benefits. Reducing the appeal of cigarettes may provide additional motivation for current smokers to quit, or switch to alternative products. Further, reducing the appeal and addictiveness of cigarettes may significantly reduce youth tobacco initiation, potentially preventing the pathway to a lifetime of addiction. However, the potential benefits for smokers must be balanced against the potential for harms to youth because of the availability of e-cigarettes and other products.

Considerations of risk and benefits of the FDA strategy are also subject to inherent uncertainties, regardless of the results of modeling intended to project the consequences. For example, the surging use of JUUL could not have been anticipated a few years ago. The tobacco product marketplace is dynamic and unstable; FDA needs to take the uncertainty of the future and the difficulties of prediction into account. And the FDA is obligated to assess overall public health impact of any new tobacco products.

We raise these general considerations around a potential nicotine standard as a reminder that reduction of nicotine content of cigarettes and other combustible products is only one element of a broader strategy. Here, with the ANPRM, we are commenting without a clear explication of that context.

General Considerations Related to a Nicotine Standard

Below, we quote directly from the ANPRM to set the context for the ATS' remarks:

"FDA is considering taking this action to reduce the level of nicotine in these products so they are minimally addictive or nonaddictive, using the best available science to determine a level that is appropriate for the protection of the public health. FDA is using the term "nonaddictive" in this document specifically in the context of a potentially nonaddictive cigarette. We acknowledge the highly addictive potential of nicotine itself depending upon the route of delivery. As discussed elsewhere in this document, questions remain with respect to the precise level of nicotine in cigarettes that might render them either minimally addictive or nonaddictive for specific members or segments of the population. We envision the potential circumstance where nicotine levels in cigarettes do not spur or sustain addiction for some portion of potential smokers.

We note that FDA is seeking to "determine a level" and posits that there is a "precise level of nicotine in cigarettes that might render them either minimally addictive or nonaddictive for specific members or segments of the population." Based on current understanding of the biological basis of nicotine addiction and the many factors driving vulnerability, we are concerned that the call for a single product standard, as stated, deviates from what is already known. On this point, the ATS offers the following comments:

We know that level of addiction to nicotine varies among individuals and across populations. How would such variation in susceptibility be addressed in the standard? Would the intent of the standard be to protect the most susceptible?

FDA will need to grapple with the critical issue of for whom the combustible product standard will be set. Is the product standard intended to prevent tobacco-naive adults from becoming addicted to combustible cigarettes, current tobacco users from satisfying a nicotine craving during quit attempts, tobacco naïve 16-year olds from becoming addicted to nicotine (or even tobacco naïve 12 year olds)? The nicotine dose that does not lead to addiction may not be consistent across age groups, ethnicities and environmental contexts given strong genetic, epigenetic and environmental drivers of nicotine addiction. Further, will the standard be set to protect the most susceptible? Would there be a margin of safety to reflect the range of susceptibility?

Any standard needs to consider both protection of youth and young adults from becoming addicted to nicotine and promoting cessation of smoking or use of noncombustible products. Would the same product standard both protect against addiction in starting smokers and motivate quitting or a move to other products?

As FDA has noted in the preamble to the proposed rule, most current adult tobacco users started smoking before they were adults. For this reason, the ATS strongly urges FDA to consider establishing a nicotine standard that is protective of pre-teen and adolescent youth, thereby providing the greatest public health protection for this large susceptible population. CDC estimates that in 2017, approximately 250,000 middle school youth used cigarettes. Considering the level of cigarette use in middle schools, targeting the nicotine standard to protect pre-teen/early teen youth from addiction is a reasonable requirement for the standard.

The ATS doubts that a clear and precise "threshold" nicotine concentration can be identified. Given the uncertainty, would FDA introduce a "margin of safety"?

There are many established models for setting standards based on scientific evidence. Most critical is the strength of the evidence supporting a particular quantitative standard and the associated uncertainties. In some regulatory contexts, e.g., the EPA's Integrated Risk Information System (IRIS) program, uncertainty is addressed by lowering guideline risk numbers by "uncertainty factors" to assure protection. Realistically, a "precise" level will not be quickly determined, yet a starting point will be needed to implement the nicotine reduction strategy. How will uncertainty be incorporated as alternatives are considered?

All Products Need to be Addressed Including Cigars and Other Combustible Tobacco Products

A reality of today's marketplace is the growth of the flavored cigar market. With mandated elimination of flavored cigarettes under the Family Smoking Prevention and Tobacco Control Act (with the notable exception of menthol as a characterizing flavor), the tobacco industry has responded by expanding the number of little cigars with characterizing flavors. CDC estimates that in 2017, 1.13 million high school youth used cigars, eclipsing high school youth cigarette use (1.12 million). Further, in 2017, over half a million high school youth used other forms of combustible tobacco including: hookahs (480,000), pipe tobacco (120,000) and bidis (100,000).

Any policy that focuses exclusively on nicotine content in combustible cigarettes, without addressing the nicotine content in other combustible tobacco products in the marketplace is incomplete at best and will not address products critical to reducing youth tobacco initiation. In fact, having a product standard only for combustible cigarettes would drive youth and young adults towards cigars and other combustible products.

Research Needs

The need for further research to support a nicotine product standard is well recognized. The path towards an evidence-based standard needs to begin with what is known about the basic biology of nicotine addiction, nicotine dosimetry and pharmacokinetics. The randomized clinical trial will have a fundamental role, but experience to date illustrates the complexities of such trials and trial findings may have limited or uncertain generalizability to the "real world" context of smoking. Once a nicotine product standard is implemented, observational data can be used to assess outcomes, particularly if the needed data collection is done prospectively.

There are potential ethical challenges to some research related to a nicotine product standard. It is not ethically possible to randomize nicotine-naïve individuals to exposure to nicotine with addiction to nicotine as a potential, or intended, outcome. This ethical constraint certainly precludes studies involving youth. Thus, evidence on nicotine concentration in products and risk for addiction cannot be addressed using the "gold standard" of the randomized clinical trial.

Regulatory Implementation

In addition to the challenges surrounding the selection of a protective standard, FDA's proposal invites many monitoring and enforcement challenges. How will FDA assure that tobacco companies are complying with an established nicotine standard? What is the definite test to establish the nicotine content of a cigarette? What is the unit of measure that FDA will use – each individual cigarette has to meet the standard? Each pack of cigarette has to meet an average per/stick standard? Each carton of cigarettes needs to meet a per/pack average? Selection of the monitoring standard may have a significant impact on the effectiveness of a nicotine standard. The ATS could envision natural or intentional nicotine concentration variation effectively undermining the effectiveness of a nicotine product standard.

Unfortunately, there is a long history of the tobacco industry re-engineering their products to deceive regulators and the public. Cigarette content has been manipulated to raise the addictiveness of nicotine. The tobacco industry used alkylating agents to raise the pH and thus increase the amount of nicotine in the more potent free base form. Lowering nicotine content should be accompanied by lowering the amount of nicotine that is delivered in the free base form, as this makes the nicotine more potent and more addictive.

The only way to reasonably measure low nicotine is to measure the total amount of nicotine contained in the tobacco leaf and in the cigarette. There is concern that the tobacco industry will manipulate cigarette size so that nicotine delivery per puff is maintained. A large margin of safety will be needed to account for differences in smoking topography. Actual nicotine delivery will vary as some smokers will smoke more intensely than others. Smoking machines to assess nicotine delivery have been shown to not be reliable, in fact the tobacco industry has designed cigarettes to deliver less nicotine to the smoking machine than in fact would be delivered to the smoker (such as by use of ventilation holes that would be open with a smoking machine but covered by the fingers of a smoker).

In conclusion, the ATS strongly recommends the agency reconsider its implicit harm reduction strategy and instead focus on a regulatory plan that addresses the harm caused by all types of tobacco/nicotine products – including initiating youth to nicotine and tobacco addiction. Further, the ATS recommends that FDA expand its vision to establish a nicotine product standard for all nicotine/tobacco products that is also customized for vulnerable communities and the larger population. We request immediate action to implement effective regulation of all tobacco products.

Sincerely,

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