

April 13, 2018

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

Re: Docket No. FDA-2018-N-0128, Nicotine Steering Committee Establishment of a Public Docket; Request for Comments

To Whom It May Concern:

The American Association for Cancer Research (AACR), with over 40,000 members, is the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication, and collaboration. We appreciate the opportunity to provide comments in response to the U.S. Food and Drug Administration's (FDA) Nicotine Steering Committee's (NSC) establishment of a public docket.

Tobacco use is the leading preventable cause of premature mortality in the United States and globally. In 2016, tobacco use caused over 7.1 million deaths worldwide due to active and secondhand smoking. In the United States, about a half million deaths from active and secondhand smoking occur every year, accounting for about 1 in 10 deaths from multiple causes. Tobacco use has a particularly profound impact on cancer incidence and mortality. Tobacco accounts for 30 percent of all cancer deaths and is causally associated with 18 different human cancers, including lung, head and neck, stomach, pancreas, colon, and cervical cancers. Continued smoking by cancer patients and survivors increases risk for overall mortality, cancer related mortality, second primary cancer, and cancer treatment toxicity. Tobacco use in any form is one of the strongest threats to public health; therefore, to curb this epidemic, we must enforce existing laws and evidence-based policies with greater vigor, invest in more research to understand nicotine addiction to inform effective control measures, and promote evidence-based policies to stem tobacco use.

The AACR applauds the FDA for placing nicotine addiction at the center of the Agency's tobacco regulatory efforts and for recognizing the continuum of risk of nicotine-containing products. Most people who use tobacco regularly do so because they are addicted to nicotine, the major addictive component in tobacco. Although most users express a desire to reduce their use

or stop entirely, overcoming nicotine addiction is difficult and may require both pharmacologic and behavioral treatments, as well as policy changes. We thank the Agency for taking this important step forward in improving public health and reducing the incidence of disease. We advocate that addressing nicotine alone, or nearly exclusively, across the FDA as a priority represents too narrow an approach. Integration of critical components associated with moderating addiction need to be considered, including behavioral counseling and medications used to ameliorate the addictive nature of tobacco, such as varenicline, bupropion, and any forthcoming medications that could moderate addiction.

In response to the FDA's Federal Register announcement, and in recognition of the significant knowledge content within the FDA's Center for Tobacco Products (CTP), the AACR provides the following comments to the NSC:

### **I. Behavior Therapies**

- Presently, there is a paucity of behavior therapies used to moderate addiction and it is important for the FDA and other federal agencies, in collaboration with the National Institutes of Health, to facilitate the development of efficacious therapies.
- Funding research into behavior therapies that facilitate completely switching to evidence-based less harmful products should be part of the charge of CTP. We feel that this makes sense given that most of the tobacco knowledge and intellectual capacity regarding tobacco resides within the CTP.

### **II. Pharmacotherapies**

- Current first-line pharmacotherapy agents that moderate addiction include nicotine replacement therapy (NRT), bupropion, and varenicline; however, other existing agents could moderate addiction and additional non-nicotine based agents are in development or are likely to be developed. The FDA should facilitate the development of new pharmacotherapies that moderate tobacco addiction. Please reference our comments below regarding loosening regulatory requirements and using smoking as the comparator (see section VI).
- Additionally, there is clear evidence that pairing pharmacotherapy with behavioral therapy leads to more success in moderating tobacco addiction. There is a dose-response relationship, such that additional counseling leads to better outcomes. Optimizing the integration of counseling across the spectrum of medical care, institutions, and providers should be encouraged and research into the reduction of barriers funded.
- The FDA should increase education and access to information on the effectiveness of methods to moderate tobacco addiction. Included should be

methods to prevent misinformation and misperceptions by providers, patients, and the general population on the utility of evidence-based moderators of tobacco addiction as well as efforts to inform on the health benefits of reducing tobacco addiction across the spectrum of health risks and outcomes.

### **III. Increasing the appeal of NRT's and use of novel products for adults**

- Originally, NRT was designed to be unappealing due to concerns about potential youth use. Unfortunately, this has led to the products being unappealing to adult patients as well. It is important for the FDA to lead the charge to create and permit NRTs that are more appealing for adults age 18 and older. Indeed, medicinal products need to be able to compete with the recreational products. It is likely that there will need to be chemical (e.g., flavors, free base nicotine, etc.) and delivery modifications to make products more appealing, as well as increased access.
- The FDA should encourage further clinical trials into electronic nicotine delivery systems (ENDS, e.g. traditional e-cigarettes and later generations of vaporized delivery devices), smokeless tobacco products, and any other forthcoming or rapidly evolving nicotine delivery devices that may be developed. This is consistent with the recent National Academy of Science, Engineering, and Medicine recommendation. Regulatory barriers to such research need to be addressed (see Section VI below).

### **IV. Regulation of product design features and packaging to prevent youth initiation of novel tobacco products**

- Increasing appeal for adults seeking to quit, which is desirable in and of itself, could have the unintended consequence of increasing appeal to youth. For example, the rapid increase in use of some products that deliver nicotine in doses similar to cigarettes shows high appeal to adults, but also to youth. It is unclear whether these devices represent a net public health benefit (by helping adults quit and keeping children off cigarettes) or harm (by addicting children to nicotine, or converting youth to smokers). Anecdotal reports of these products suggest a possible cause for concern that requires continued monitoring and evaluation of the net public health effects of these products on adults and youth, and consideration of regulatory actions based on emerging empirical data. While monitoring the possible public health benefits (which will take some time), at present it is essential that the FDA implement regulatory measures to minimize access by youth under age 18 to highly appealing and potentially addicting nicotine delivery systems. It may be that the availability of e-cigarettes to youth will decrease the number of youth cigarette smokers who uptake e-cigarettes instead, but this concept remains speculative. There are some data to suggest a harmful effect for e-cigarette use on developing brains, and there remains

speculation about youth e-cigarette users transitioning to smoking. The AACR believes that the FDA should follow the precautionary principle and strive to reduce youth access and use unless there are sufficient data to indicate a net public health benefit.

**V. Tobacco mixed with other substances**

- The FDA needs to recognize that the tobacco landscape is changing dramatically and the FDA needs to make sure that they are aware of these products that can be used for non-tobacco substances in the future. These are the products consumers will be shifting toward and the FDA needs to be ready to address products that will target a growing population of consumers.

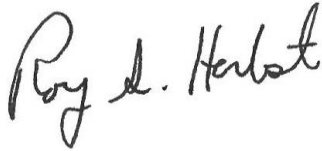
**VI. Minimizing regulatory burdens in the development and evaluation of new cessation products**

- It is crucial for the FDA to consider practical issues and methods associated with requirements for an Investigational New Drug/Investigational Tobacco Product (IND/ITP) as related to the development and testing of new tobacco related products. Current IND/ITP procedures are very difficult for academic investigators and prevent academic research of important investigations that are critical to understanding use, toxicology, and health outcomes. Because of rapid developments in the product and use spaces, current IND/ITP procedures will result in delays in testing products and will subsequently result in migrating use patterns before being able to accurately assess use or health effects in a well-designed monitored environment. For example, for products that have been in the marketplace for years, the FDA should loosen the toxicology, chemistry, and manufacturing requirements.
- Related to tobacco product development, the ability to obtain INDs needs to be reframed in the context of existing product comparators, such as combustible tobacco. Product safety for ENDS in particular should be considered in the comparative context of the substantial risks associated with smoking. Reliance on preclinical data and standard clinical trial designs could be a significant barrier to understanding ENDS and tobacco specific questions, such as use and health effects in the context of continued tobacco use.
- There should be a rapid review and decision on new tobacco treatment products.

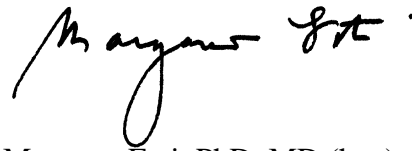
In conclusion, the AACR commends the FDA on their comprehensive plan that places nicotine addiction at the center of the Agency's tobacco regulatory efforts. Thank you very much for considering our input on this important issue. These comments are based on careful discussion and evaluation of the extant literature on tobacco treatment by the AACR's Tobacco and Cancer Subcommittee (roster attached), and are approved by the AACR's CEO and Chairs of the Tobacco and Cancer Subcommittee and Science Policy and Government Affairs Committee. If

the AACR can provide any additional information or assistance to the FDA, please do not hesitate to contact Nicole Boschi, PhD, Senior Science Policy Analyst, at 215-446-7275 or [nicole.boschi@aacr.org](mailto:nicole.boschi@aacr.org).

Sincerely,



Roy S. Herbst, MD, PhD  
Chair, Tobacco and Cancer Subcommittee  
American Association for Cancer Research



Margaret Foti, PhD, MD (h.c.)  
Chief Executive Officer  
American Association for Cancer Research



George D. Demetri, MD  
Chair, Science Policy and Government Affairs Committee  
American Association for Cancer Research

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The University of Texas M. D. Anderson Cancer Center  
Houston, Texas

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Vice President & Division Head, Div. of Cancer  
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The University of Texas M. D. Anderson Cancer Center

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Division Head, Cancer Medicine  
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The University of Texas MD Anderson Cancer Center

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Health (REACH)  
Mayo Clinic Cancer Center

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Professor, College of Medicine  
The Ohio State University Medical Center

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Associate Professor of Public Health Sciences  
Chief of Tobacco Cessation and Health Behaviors  
Co-Director, Lung Cancer Screening Program  
Hollings Cancer Center  
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### **Kasisomayajula (Vish) Viswanath, PhD**

Associate Professor  
Department of Society, Human Development, and Health  
Harvard School of Public Health  
Associate Professor of Population Sciences  
Department of Medical Oncology  
Dana-Farber Cancer Institute

### **Graham Warren, MD, PhD**

Associate Professor  
Vice Chairman for Research in Radiation Oncology  
Hollings Cancer Center  
Medical University of South Carolina