

February 1, 2019

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

Re: Docket No. FDA-2018-N-3952, Eliminating Youth Electronic Cigarette and Other Tobacco Product Use: The Role for Drug Therapies; Public Hearing; Request for Comments

To Whom It May Concern:

The American Association for Cancer Research (AACR), with over 40,000 members, is the first 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) notification of public hearing; request for comments: Eliminating Youth Electronic Cigarette and Other Tobacco Product Use: The Role for Drug Therapies; Public Hearing; Request for Comments.

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 remaining committed to the agency's Youth Tobacco Prevention Plan. Nearly all tobacco use begins in youth and young adulthood and, since 2014, e-cigarettes have

been the most commonly used tobacco product among youth. The AACR shares the FDA's concern that e-cigarette products are addicting a new generation to nicotine and that the rise in youth e-cigarette use may translate to later use of combustible cigarettes. Unfortunately, we do not have a good scientific understanding of many of the questions that the FDA is asking in this notice. For example, we do not fully understand the characteristics of youth nicotine dependence or of the youth e-cigarette user and their motivations to quit using nicotine-containing products.

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:

1. *FDA notes that the factors driving e-cigarette use among youth likely differ from those in the adult population. How might such differences impact the need for, or use of, drug therapies for e-cigarette cessation among youth?*

Although youth are likely to differ from adults in their motivations to initiate use of e-cigarettes, we do not have a full understanding of the characteristics of youth nicotine use or the nicotine dependence phenotype in this population. Additionally, we do not have a full understanding of the youth e-cigarette user, their patterns of e-cigarette use, or their motivation to seek out cessation therapies. Nicotine replacement therapies (NRTs) have shown reduced efficacy in youth relative to adult tobacco users. This may suggest that youth tobacco use is less driven by physiological dependence and more by psychosocial factors (e.g. social engagement). Therefore, it is unclear if there is a need to use medications to achieve e-cigarette cessation or if behavioral tools for cessation would be more effective.

The AACR stresses the need for more research into the factors driving youth e-cigarette use, youth dependence on e-cigarettes, and their motivation to quit.

2. *FDA is interested in whether there is a population of youth e-cigarette users who would be likely to benefit from the use of drug therapies for e-cigarette cessation. What age groups (older adolescent vs. younger adolescent), patterns in tobacco use (duration and frequency of use), and clinical features (level of addiction, presence/absence of comorbidities including psychiatric disease) might characterize this population? What types of products (NRT vs. non-NRT; prescription vs. over-the-counter) might be useful?*

As stated in our response to question 1, we do not currently know how motivated the youth population is to quit using e-cigarettes. However, since pharmacotherapies are designed to address physiological nicotine dependence (i.e. reduce withdrawal symptoms and cravings), it would be logical that they would work best on the most nicotine-dependent vapers. Most likely, this population would include those who use nicotine products more frequently, have used these products for a longer period, and who engage in nicotine use behaviors across a wider variety of situations (i.e. non-social and social cigarette/e-cigarette users). Given our

lack of understanding, we can only posit that a dual treatment strategy (i.e. behavioral counseling and pharmacotherapy) would be a potential treatment option.

- 3. Describe the scientific, clinical, and societal factors that could either encourage or impede the conduct of clinical trials designed to evaluate drugs intended for youth e-cigarette cessation. What approaches could be used to encourage research and overcome barriers to research?*

The greatest challenge for clinical trials designed to evaluate drugs intended for youth e-cigarette cessation is motivating adolescents to engage in such a clinical trial and obtaining consent from parents, since youth may not want their parents to know about their e-cigarette use. In addition, the restricted indications for use of current medications may provide a challenge for youth who may be interested in using these cessation products. For example, instructions for youth use may be quite different from that of adult use.

Another consideration is that it may be possible to manipulate nicotine doses of e-cigarette fluids as a method to help adolescents become less dependent on e-cigarettes and therefore facilitate cessation attempts and success. However, because a master file is needed to do such a study, it would make conducting this type of trial impossible for academic researchers.

Current IND 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 procedures will result in delays in testing products and will subsequently result in migrating use patterns before researchers are 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. It is crucial for the FDA to consider practical issues and methods associated with requirements for an IND as related to the development of new and novel nicotine cessation therapies. Finally, there should be a rapid review and decision on new tobacco treatment products.

- 4. What methods and study designs are appropriate for assessing drug therapies for youth e-cigarette cessation? What are the appropriate control groups? What are the most informative endpoints and the best assessment tools to evaluate these endpoints?*

A randomized clinical trial would be appropriate for adolescents. Since it is possible that behavioral treatment is sufficient for adolescents, the control group would be placebo medication. Both treatment and placebo groups should receive adolescent-relevant psychosocial intervention. Endpoints could be e-cigarette and tobacco-free days, past month without use of any tobacco product including e-cigarettes, and continuous abstinence from e-

cigarette/tobacco products with a grace period. Endpoints could be biomarkers of exposure, health effects (e.g., respiratory symptoms), and cognitive effects. It is possible that another method of treatment could be either a gradual or immediate reduction in the levels of nicotine in e-cigarette cartridges to 0 mg. This method could be compared to conventional NRT. However, given the concern regarding the effects of nicotine on the developing brain, conventional NRT may not be the most appropriate comparator.

- 5. Acknowledging that to date research has been limited, are there data available from the adult experience with smoking cessation that could potentially be leveraged in the effort to develop drug therapies for youth e-cigarette cessation? Have any drug therapies demonstrated potential to help adults discontinue e-cigarette use? Are there differences between adolescents and adults that impact the ability to extrapolate efficacy findings from the adult population to the adolescent population? Could existing NRT products be useful for youth e-cigarette cessation?*

We believe that there are not enough data to sufficiently answer this question as we do not have a clear understanding of the motivation surrounding e-cigarette cessation. Behavioral and other nonpharmacological therapies have shown some promise and may be more appropriate for youth populations as current literature has shown that, even when youth are nicotine dependent, NRTs have very little effect on cessation. We also do not have enough data to determine the best method to help adults quit using e-cigarettes. Pharmacological cessation tools for adults could include current medications for smoking cessation or, as proposed above, and a gradual or immediate reduction in nicotine doses of electronic cigarettes to 0 mg of nicotine in e-cigarette cartridges.

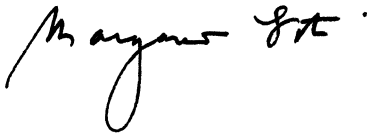
- 6. While this hearing is focused on the topic of e-cigarette use among youth, as e-cigarettes are currently the most commonly used form of tobacco in this population, FDA also welcomes comments regarding the potential need for drug therapies to support cessation of other tobacco products, including combustible products (i.e., cigarettes or cigars) and smokeless tobacco products, among youth and the issues impacting the development of such therapies.*

Although the AACR is concerned about e-cigarette use in youth populations, given that combustible cigarettes remain the most dangerous tobacco products in terms of public health, we suggest that the FDA's focus remain on those products. Additionally, we suggest that the FDA focus on achieving a less nicotine-dependent population by reducing the addictiveness of combustible tobacco products.

In conclusion, the AACR commends the FDA on their Youth Tobacco Prevention Plan and for convening a public hearing to examine strategies for eliminating youth e-cigarette and other tobacco product use. 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.

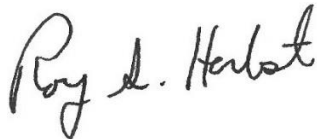
Sincerely,



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Comments on Eliminating Youth Electronic Cigarette and Other Tobacco Product Use from the American Association for Cancer Research (AACR)

- The American Association for Cancer Research (AACR), with over 40,000 members, is the first and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication, and collaboration

The AACR Tobacco and Cancer Subcommittee was convened in 2009 to foster scientific and policy initiatives to reduce the incidence of disease and mortality due to tobacco use

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- Factors Driving Youth E-Cigarette Use
- Cessation Strategies for Youth Nicotine Users
- Factors that could encourage or impede the conduct of clinical trials designed to evaluate drugs intended for cessation

Factors Driving Youth E-Cigarette Use

- Youth generally differ from adults in their daily e-cigarette use.
- Youth actively engage in social media, which has allowed rapid exchange of information on products, including where to obtain e-cigarettes.
- Adolescent brains are still developing and youth users are very different than the adult e-cigarette user.
- We do not have a full understanding of the prevalence / characteristics of nicotine use or what nicotine dependence looks like in youth. Additionally, we do not have a full understanding of the youth e-cigarette user or patterns of youth e-cigarette use.
- We do not know whether nicotine-dependent youth want to quit.

- We need to better understand youth motivation to quit nicotine use and how to motivate this population to seek out cessation assistance.
- The AACR recommends a dual treatment strategy for youth combustible tobacco and e-cigarette users.
 - Counseling and behavioral therapy - behavioral counseling is critical for the success of pharmacotherapy. At a minimum, there should be behavioral counseling as part of any strategy for cessation.
 - Perhaps pharmacotherapy should be used in youth, where appropriate.

Use of NRTs in Youth Tobacco Users

- There is evidence that levels of nicotine dependence may be lower in young smokers relative to the adult population (Rubinstein, 2007).
- Even when youth are nicotine dependent, the data on the efficacy of NRTs are equivocal at best.
- A 2017 Cochrane review (Fanshawe et. al, 2017) found little evidence of pharmacotherapy effectiveness in adolescent regular tobacco users under age 20:
 - only group counseling and behavioral interventions showed promise.
 - there was not enough evidence to recommend widespread implementation of any particular youth tobacco cessation method.

Factors that Encourage / Impede Clinical Trials Designed to Evaluate Drugs Intended for Youth E-Cigarette Cessation

- The AACR believes that it is crucial for the FDA to consider practical issues associated with requirements for an Investigational New Drug/Investigational Tobacco Product (IND/ITP) as related to the development of new 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.
- 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.
- AACR recommends that NIH and FDA take into consideration that recruitment of youth into clinical trials is far more costly and time consuming than when recruiting adults, thus making the cost greater than most NIH funding mechanisms.
- Additionally, the AACR recommends a rapid review and decision on new tobacco treatment products.

Summary

- The AACR commends this effort by the FDA; however, we believe that there is not enough scientific evidence to answer the questions the FDA poses. We do not have a full understanding of the characteristics of youth e-cigarette users, patterns of e-cigarette use, and dependence on the product.
- More research is needed on nicotine dependence, ways to increase motivation to quit, and the role of NRTs in youth populations.
- The AACR recommends a rapid review and decision on new tobacco treatment products.
- Although the AACR is concerned about youth e-cigarette use, we suggest that the FDA remain focused on a reduction in the use of combustible products and on generally achieving a less nicotine-dependent population.

For questions, please contact Nicole Boschi, PhD, Senior Science Policy Analyst, at 215-446-7275 or nicole.boschi@aacr.org