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January 30, 2019

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

RE: Written comments in connection with January 18, 2019 public hearing on “Eliminating Youth Electronic Cigarette and Other Tobacco Product Use: The Role for Drug Therapies,”
Docket No. FDA-2018-N-3952

The Campaign for Tobacco-Free Kids (Tobacco-Free Kids) submits these comments in the above-referenced Docket established in connection with the January 18, 2019 public hearing convened by the U.S. Food and Drug Administration (FDA) on the Role for Drug Therapies in Eliminating Youth Electronic Cigarette and Other Tobacco Product Use. 83 Fed. Reg. 64752 (December 18, 2018).

The Current Epidemic of Youth E-Cigarette Usage and Nicotine Addiction

The FDA is to be commended for recognizing, in recent months, that our nation faces a public health crisis arising from the meteoric rise in the use of e-cigarette products by young people. FDA Commissioner Gottlieb has said current usage rates by youth have reached “epidemic” proportions,¹ an assessment recently joined by the U.S. Surgeon General.² The data recited by Dr. Gottlieb in convening the January 18 hearing are beyond alarming: from 2017-2018, a 78% increase in current e-cigarette use among high school student and a 48% increase among middle school students, meaning that 3.6 million middle and high school students currently use e-cigarettes, an increase of 1.5 million in one year alone.³ No longer is there any doubt that the current epidemic represents far more than youthful “experimentation” with e-cigarettes. As the Commissioner’s statement pointed out, more than a quarter of current high school e-cigarette users are using these products regularly; that is, on 20 or more days in the past month.⁴ This is clear evidence of addiction, not experimentation.

¹ See Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency’s continued efforts to address growing epidemic of youth e-cigarette Use, including potential new therapies to support cessation (November 2, 2018).

² Surgeon General’s Advisory on E-Cigarette Use Among Youth (December 18, 2018) (SG Advisory).

³ Remarks by Scott Gottlieb, M.D., Public Hearing on Eliminating Youth Use of Electronic Cigarette and Other Tobacco Product Use: The Role for Drug Therapies (January 18, 2019) (Gottlieb remarks).

⁴ Id.

We agree with the conclusion of the Commissioner that the situation is sufficiently serious that it is necessary to convene a hearing to explore the potential role of drug therapies in responding to the current epidemic. In his statement, Dr. Gottlieb referred to the “painful stories from parents of teenagers, pediatricians, and young people themselves” that “make clear that, for many young e-cigarette users, addiction has already taken hold.”⁵ The epidemic of e-cigarette use is, as Commissioner Gottlieb said last September, “an epidemic of addiction.”⁶

There is no doubt that the rise of adolescent e-cigarette use in the past year to epidemic proportions is due to the remarkable appeal to this age group of a novel pod-based e-cigarette design, a market dominated by Juul. Indeed, in October, Department of Health and Human Services Secretary Azar and FDA Commissioner Gottlieb, in an op-ed in *The Washington Post* about the “epidemic” of e-cigarette use among young people, pointed to Juul’s 70% share of the cartridge-based market,⁷ dominance that has only grown since that time. U.S. Surgeon General Jerome Adams, in a rare Advisory, issued December 18, cited the 600% increase in Juul sales during 2016-17 and described the features of these products that are so appealing to young people, including their minimal exhaled aerosol, reduced odor, small size, and similarity in appearance to a USB flash drive, making them easy to conceal from parents and teachers.⁸ Moreover, Juul, like other e-cigarettes, has been marketed with kid-friendly flavors. As Commissioner Gottlieb noted in his statement at the January 18 hearing, more than two-thirds of regular high school e-cigarette users are using flavored products.⁹

There is no question that Juul is highly addictive. The Surgeon General noted Juul’s “high level of nicotine,” with a typical Juul cartridge, or “Juulpod,” containing about as much nicotine as a pack of 20 regular cigarettes.¹⁰ He also pointed to Juul’s use of “nicotine salts, which allow particularly high levels of nicotine to be inhaled more easily and with less irritation” than the nicotine traditionally used in tobacco products, including other kinds of e-cigarettes. “This is of particular concern for young people,” the Surgeon General warned, “because it could make it easier for them to initiate the use of nicotine through these products and also could make it easier to progress to regular e-cigarette use and nicotine dependence,” although studies show that “approximately two-thirds of Juul users aged 15-24 are unaware that Juul always contains nicotine.”¹¹

The epidemic use of e-cigarettes by adolescents has profound public health consequences. The Surgeon General’s Advisory warns that “[n]icotine exposure during

⁵ Id.

⁶ Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use” (Sept. 12, 2018).

⁷ Alex M. Azar and Scott Gottlieb, “We cannot let e-cigarettes become an on-ramp for teenage addiction,” *Washington Post* (October 11, 2018).

⁸ SG Advisory, at 1-2.

⁹ Gottlieb remarks, at 3.

¹⁰ SG Advisory, at 2.

¹¹ Id.

adolescence can harm the developing brain,” impacting “learning, memory and attention.”¹² Moreover, according to a 2018 report of the National Academy of Sciences, Engineering and Medicine, “There is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults.”¹³ Thus, the current e-cigarette youth epidemic threatens to undermine the historic gains in reducing youth smoking made over the last several decades. But, as the Surgeon General has said, “any e-cigarette use among young people is unsafe, even if they do not progress to future cigarette smoking.”¹⁴

The Need for Research to Better Understand How to Address Youth Nicotine Addiction

In his statement convening the January 18 hearing, Dr. Gottlieb commented that “[a]lthough there is a large body of research on adult smoking cessation, the methods to treat adolescents and teens who’re addicted to vaping are not well understood.”¹⁵ He added “[t]here is little information about how drug or behavioral interventions might support youth e-cigarette cessation, as well as youth tobacco use more generally.”¹⁶

The expert testimony delivered at the hearing confirms the dearth of data and understanding about the treatment of youth nicotine addiction. As Dr. Susanne E. Tanski, representing the American Academy of Pediatrics (AAP), noted in her statement at the hearing, “unfortunately, little research has been conducted assessing the effectiveness of pharmacologic therapies such as nicotine replacement therapy, varenicline, and bupropion for smoking cessation in adolescents.”¹⁷ She further noted that, due to insufficient evidence of efficacy, nicotine replacement therapy (NRT) for adolescent smoking cessation was not recommended in the most recent guidelines of the U.S. Preventive Services Task Force and has not been approved by FDA for use with patients under the age of 18.¹⁸ Moreover, she pointed out that, in contrast to traditional combusted cigarettes, “we currently know very little about the trajectories of nicotine dependence for e-cigarettes.”¹⁹ and there is virtually no data on treatment of adolescents with e-cigarette dependence.²⁰ Dr. Tanski stated: “In particular, we need the help of FDA to identify how best to treat young people who are already dependent on high-nicotine-delivery products

¹² Id., at 1.

¹³ National Academies of Sciences, Engineering, and Medicine, *Public health consequences of e-cigarettes.*, Washington, DC: The National Academies Press, 2018, <http://nationalacademies.org/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx>.

¹⁴ SG Advisory, at 1.

¹⁵ Gottlieb remarks, at 4.

¹⁶ Id.

¹⁷ Statement of Susanne E. Tanski, MD, MPH, FAAP on behalf of the American Academy of Pediatrics before the Food and Drug Administration, Public Hearing on “Eliminating Youth Electronic Cigarette and Other Tobacco Product Use: The Role of Drug Therapies,” January 18, 2019 (Tanski statement), at 3. See also Bonnie Halpern-Felsher, Ph.D., “What FDA should do to reduce youth addiction to e-cigarettes,” presentation to January 18 FDA hearing, slide 2 (Halpern-Felsher statement).

¹⁸ Tanski statement at 3.

¹⁹ Id.

²⁰ Id. at 2.

like JUUL.”²¹ It is particularly troubling that, as Dr. Tanski noted, recent studies have shown higher concentrations of urinary cotinine levels in users of pod-based systems like Juul as compared to teens using conventional combusted cigarettes.²²

Therefore, we join AAP and others in calling on FDA to fund studies to better understand adolescent nicotine addiction, while also quickly identifying effective interventions for the adolescent population of e-cigarette users.

FDA Must Take Stronger Action to Prevent Youth Addiction to E-Cigarettes

It is readily apparent that any action FDA takes to respond to the current population of teens who are struggling with addiction to Juul and other e-cigarette products will be undercut if that population continues to grow. Therefore, in addition to exploring all possible ways to use its authority to respond to the needs of already-addicted teens, the agency needs to take much stronger action to regulate e-cigarettes and their marketing to bring the current epidemic under control.

To date, FDA’s primary regulatory response has been focused on restricting access to certain flavored e-cigarette products by requiring that they be sold in adult-only physical locations, as well as sold on-line only with heightened age-verification processes.²³ Although access restrictions are important, given the intense appeal of Juul and similar flavored products to teens, and the extent of the current epidemic, access restrictions alone are not likely to be sufficient. As long as these appealing, flavored products are on the market, young people will find ways to obtain them.

Therefore, FDA should move quickly to implement a stronger regulatory response to the current epidemic.

First, it must exercise its statutory authority to take off the market all non-tobacco flavored e-cigarettes that meet the definition of “new tobacco products” under the Family Smoking Prevention and Tobacco Control Act (TCA) (i.e. they entered the market after February 15, 2007) and do not have marketing orders from FDA, as required by Section 910 of the TCA. FDA does not dispute that there is no statutory authorization for such products to remain on the market without agency public health review; their continued sale without marketing orders is allowed only due to FDA’s current “compliance policy,” announced in its August, 2017 Guidance for Industry,²⁴ which the agency can, and should, reverse. There is no public health

²¹ Id. at 2.

²² Id. at 3-4.

²³ See Statement from FDA Commissioner Scott Gottlieb, M.D., on proposed new steps to protect youth by preventing access to flavored tobacco products and banning menthol in cigarettes, November 15, 2018 (Gottlieb November 15 statement).

²⁴ U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule, Guidance for Industry (Revised) (August, 2017).

justification to allow flavored e-cigarettes, which have proven so appealing to young people, to remain on the market without FDA review until August, 2022, as the epidemic of youth nicotine addiction continues unabated. FDA should also expedite issuance of a proposed and final rule establishing a product standard prohibiting non-tobacco characterizing flavors in all tobacco products, including menthol in cigarettes.

Second, FDA must enforce the statutory premarket review requirement against products that have entered the market after the effective date of the deeming rule (August 8, 2016) without marketing orders; such products have never been legally marketed under the current compliance policy, which applies only to products already on the market as of that date. FDA has acknowledged that it has received complaints²⁵ about products with new “features, formulations or flavors” apparently introduced after August 8, 2016 without receiving a premarket order as required by the TCA and has sought information from manufacturers about forty products showing that they were on the market as of that date and have not been modified since that time.²⁶ It is critical that FDA enforce the law against companies found in violation of the premarket review requirement and that it require all e-cigarette manufacturers to submit evidence that their products were on the market as of August 8, 2016.

Third, FDA must take immediate action against all non-tobacco flavored e-cigarette products, including menthol and mint. FDA’s proposed access restrictions do not apply to menthol and mint flavors. However, as use of flavored e-cigarettes by high school students increased from 60.9% to 67.8% from 2017-2018, use of menthol or mint-flavored e-cigarettes increased from 42.3% to 51.2%.²⁷ Thus, FDA’s current policy does nothing to even reduce access to certain flavored products with a well-established appeal to youth.²⁸ FDA should take off the market all non-tobacco flavored e-cigarette products, including menthol and mint, until they are subject to FDA public health review.

Fourth, FDA should place a moratorium on on-line sales of all e-cigarette products, regardless of flavorings, until on-line sellers can demonstrate the use of effective age verification systems to prevent sales to youth.

²⁵ For example, on August 7, 2018, Tobacco-Free Kids, along with other public health groups, wrote to Commissioner Gottlieb about the recent entry into the market of numerous products similar in design to Juul, that had not received premarket orders, including products marketed by leading cigarette companies Altria, ITG Brands and R.J. Reynolds, as well as other products introduced by independent manufacturers. In addition to Tobacco-Free Kids, the letter was signed by the American Academy of Pediatrics, the American Cancer Society Cancer Action Network, the American Heart Association, the American Lung Association and Truth Initiative.

²⁶ FDA News Release, FDA advances investigation into whether more than 40 e-cigarette products are being illegally marketed and outside agency’s compliance policy,” (October 12, 2018).

²⁷ U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, “Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students – United States, 2011-2018”, MMWR, Vol. 67, No. 45 (November 16, 2018).

²⁸ See Halpern-Felsher presentation, slide 12.

Fifth, FDA must take action against any e-cigarette product marketed in ways that make them appealing to young people. Commissioner Gottlieb has cited the use of children’s cartoon or animated characters, or the use of kid-appealing brand names, as examples of such marketing,²⁹ but it is clear that e-cigarette companies have been using far more sophisticated and effective ways of marketing their products to a broader audience of kids, including teens. Juul’s spectacular success in attracting the youth market was not an accident and was not a result of the product’s features alone. Rather, as a recent Stanford University study shows,³⁰ Juul was launched with social media and other advertising using images that overtly targeted young people and, indeed, mimicked the imagery long used by cigarette companies to appeal to youth. FDA must impose on e-cigarettes all the marketing restrictions that currently apply to cigarettes and must actively monitor e-cigarette marketing to expose, and take action against, marketing of these products using techniques and strategies calculated to reach large numbers of young people with appealing images and messaging.

FDA Should Act Proactively to Maximize the Public Health Impact of Existing FDA-Approved Smoking Cessation Medications for Adults and to Help Stimulate Innovation in Smoking Cessation Medicines for Adults

As FDA addresses the potential for drug therapies and other interventions to address the current crisis in youth e-cigarette addiction, it should also recognize the reality that currently-approved FDA smoking cessation medicines have proven insufficient to help millions of adults currently addicted to cigarettes. In 2015, 67% of smokers reported that they want to quit and 55.4 percent of smokers made a quit attempt during that year.³¹ However only 7.4% had actually quit during the year.³² Though studies show higher success in quitting among those who use some form of approved medication, only one-third of smokers use any of those medications when making a quit attempt.³³

Commissioner Gottlieb repeatedly has recognized the need for greater innovation in the development and use of smoking cessation medications. For example, in his statement issuing the Draft Guidance on Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products on August 3, 2018, the Commissioner noted that most of the existing NRTs were approved more than twenty years ago, citing the need “to explore what steps we can take using our regulatory policies to enable opportunities for innovation, while making sure these products are demonstrated to be safe and effective for their intended use.”³⁴

²⁹ Gottlieb November 15 statement, at 9.

³⁰ Jackler, Robert K. et al., “JUUL Advertising Over its First Three Years on the Market” (January 24, 2019).

³¹ Babb S, Malarcher A, Schauer G, Asman K, Jamal A. “Quitting Smoking Among Adults — United States, 2000–2015,” *MMWR Morb Mortal Wkly Rep* 2017;65:1457–1464.

³² Id.

³³ Id.

³⁴ U.S. Dept. of Health and Human Services, Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps the agency is taking to support the development of novel nicotine replacement drug therapies to help smokers quit cigarettes (August 3, 2018).

We believe FDA needs to do a comprehensive review of how its Center for Drug Evaluation and Research (CDER) regulates products already approved for smoking cessation and assess how it can encourage the development and approval of innovative new products that will be more effective and reach more smokers. We refer the agency to the letter submitted to Commissioner Gottlieb on December 20, 2018 by Tobacco-Free Kids and other public health and medical groups, along with nine leading experts in smoking cessation and related research, setting out a detailed CDER reform agenda. The letter, attached as an exhibit to these comments, makes the following specific recommendations:

- FDA should create a regulatory environment and pathway that encourages and facilitates responsible companies' efforts to produce and market new and more effective smoking cessation products.
- In assessing the risks vs. benefits of smoking cessation products, FDA must make it clear that continued smoking is the relevant comparator.
- FDA should take proactive steps to demonstrate its willingness to consider new indications and labeling changes for existing smoking cessation products.
- FDA should take affirmative steps to explore alternatives to long-term clinical trials for promising new products or for new indications for existing products, where sufficient evidence is available to meet both the safety and efficacy standards without long-term clinical trials.
- FDA should establish criteria for the use of accelerated pathways to approval for promising smoking cessation drugs.
- FDA should evaluate whether to modify its current organizational structure to create a new environment of innovation to confront the epidemic of smoking-related disease.

Therefore, as FDA seeks answers to the important questions surrounding the treatment of nicotine addiction among young people, it should not be satisfied with the currently approved treatments for adults and should proactively seek to create a new regulatory environment of innovation in the uses of existing approved drugs and the development of new treatments.

Respectfully submitted,

Campaign for Tobacco-Free Kids

December 20, 2018

Dr. Scott Gottlieb
Commissioner
U.S. Food and Drug Administration
White Oak Building One
10903 New Hampshire Ave.
Silver Spring, MD 20993

Dear Dr. Gottlieb:

We write concerning the urgent need for the Food and Drug Administration (FDA) to move quickly toward a fresh look at, and new approach to, the evaluation of drug therapies for smoking cessation. As the result of your announcement in July 2017 of a comprehensive plan for reducing the death and disease caused by tobacco, and your recent announcement of initiatives to prohibit mentholated cigarettes and flavored cigars, now more than ever there is a need for a review of how the Center for Drug Evaluation and Research (CDER) regulates products already approved for smoking cessation, and for FDA to encourage the development and approval of products that will be even more effective and reach even more smokers.

As researchers, smoking cessation experts, and tobacco policy advocates, we have long been concerned about restrictions placed on the labeling and use of existing smoking cessation products, as well as the structural and regulatory barriers that may discourage the development of new, more effective drugs. We have been encouraged by your July 2017 announcement of a “new and comprehensive” plan for nicotine regulation and your recognition that for the plan to succeed, there is a need to do more to help smokers quit, including the need for greater innovation in therapeutic products. Your convening of a cross-agency Nicotine Steering Committee and the hearing in January 2018 were important steps forward. But we have yet to see bold action that reflects the sense of urgency your words correctly conveyed. Today, it is our collective view that the need for action is paramount.

This urgent need for action has brought us together to urge science-based actions that FDA could take that are strongly supported by a broad cross section of experts in the field. By this letter, we take the first step in proposing an agenda for reform.

It is our view that FDA should proactively establish policies and processes based on the available evidence to maximize the public health impact of existing products and create a new environment of innovation for smoking cessation products. FDA need not wait for product manufacturers to submit new drug applications (NDAs) or supplemental NDAs for particular products, but can proceed independently.

We are prepared to work with the agency to examine the evidence in support of these recommendations. To do so, we request a meeting, as soon as possible, with you and senior staff at CDER and the Center for Tobacco Products (CTP), to be attended by a subgroup of the undersigned, to discuss how to move forward the reforms suggested by this letter.

FDA Policy Toward Smoking Cessation Products Must Recognize Smoking-Related Disease as a National Epidemic Requiring Urgent Attention.

In your July 2017 announcement, you spoke of the need to take on addiction to nicotine as a public health problem with the same vigor that FDA is addressing the epidemic of opioid addiction. You also noted that upwards of 480,000 premature deaths are caused by cigarette smoking every year, the leading preventable cause of death in the U.S. Without minimizing the dimensions of the opioid tragedy, the annual death toll from smoking is approximately 15 times that from opioid overdoses. In August 2018, you recognized that “[a]s a public health agency, there is no greater impact we can have to improve the health of our nation than to significantly reduce the rate of tobacco-related disease and death.”

The disease and death from smoking must be treated as the public health epidemic that it is. This tragic epidemic should spur FDA’s efforts to revisit its approach to cessation medications with unprecedented commitment. In your statement issuing the Draft Guidance on Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products on August 2, 2018, you noted that most of the existing nicotine replacement therapies (NRTs) were approved more than twenty years ago, and cited the need “to explore what new steps we can take using our regulatory policies to enable opportunities for innovation, while making sure these products are demonstrated to be safe and effective for their intended use.” Moreover, as to non-nicotine medicines, the pace of innovation also has been slow, with no new medications approved in the last ten years. Thus, steps to encourage innovation should address not only NRTs, but other non-nicotine cessation products as well.

FDA has demonstrated its ability to respond urgently to other public health crises like opioid addiction, HIV AIDS, and cancer. As you and Secretary Azar so aptly wrote in your October 11, 2018 Washington Post Op-Ed about reducing tobacco use:

The efforts at HHS to combat tobacco's lethality focus on two key goals: First, reducing the nicotine levels in combustible cigarettes to render them minimally or nonaddictive. Second, harnessing new forms of nicotine delivery, including medicinal products and e-cigarettes, to give adult smokers less harmful substitutes for cigarettes.

This will only happen if CDER takes the type of actions recommended in this letter.

FDA Should Create a Regulatory Environment and Pathway That Encourages and Facilitates Responsible Companies’ Efforts To Produce and Market New and More Effective Smoking Cessation Products.

Given the death toll from tobacco and the large potential market for smoking cessation treatments (the more than 36 million American smokers), the fact that so few cessation products have been approved in the last twenty years underscores the need for FDA to make changes to create and maintain an environment that results in more companies investing in the development and pursuit of FDA approval for new safe and effective cessation products. Particularly with the explosive emergence and widespread use of e-cigarettes in recent years, it has become plain that the current regulatory structure rewards companies for marketing a wide variety of e-cigarettes and other nicotine products to as many consumers as possible for recreational use. Yet there are substantial disincentives – like high costs and substantial delays – for companies to pursue FDA approval of drugs backed by good science that are safe and effective at helping smokers quit.

FDA has the authority to respond to this current imbalance through a coordinated agency-wide effort that must include a careful assessment of the barriers faced by responsible companies who wish to pursue the CDER pathway to market. That assessment should include an examination of the time and expense required to obtain approval as a drug, particularly for new nicotine products that are similar to products for which an extensive base of knowledge about their effects already exists, based on their use in the U.S. and in other countries.

In Assessing the Risks vs. Benefits of Smoking Cessation Products, FDA Must Make It Clear That Continued Smoking Is the Relevant Comparator.

Despite certain public statements to the contrary, CDER has not approached smoking cessation as a treatment for a disease that kills 480,000 Americans needlessly every year. Cigarettes kill half of their long-term users, and millions of smokers suffer from debilitating smoking-related diseases. Quitting smoking rapidly and dramatically lowers the death toll. Thus, when assessing the risks of new indications or labeling changes for existing approved products, or the safety of new products, FDA must compare the risks posed by the cessation therapy to the risks posed by continued smoking.

CDER should recognize that smokers who don't quit will continue to be at significant risk for tobacco-related disease and death. Evaluating a product with this in mind does not, of course, require CDER to compromise its safety standards, but rather ensures appropriate consideration for the ultimate risks from continued smoking. FDA has long assessed product safety and risk in the full context of the condition for which it is used. As one example, certain cancer therapies may themselves be toxic or cause serious side effects, yet be important treatments for patients suffering from debilitating cancers. Not only must FDA use continued smoking as the relevant comparator, it should also make it clear to the pharmaceutical industry, and the public, that it will do so in assessing the risks posed by smoking cessation products that are the subject of NDAs submitted to CDER.

FDA Should Take Proactive Steps To Demonstrate Its Willingness To Consider New Indications and Labeling Changes for Existing Smoking Cessation Products.

In your Statement accompanying FDA's Draft Guidance on orally-inhaled nicotine products, you referred to a future guidance that will "help lay out a framework for new potentially clinically relevant outcomes for smoking cessation products, such as reducing the chance of a smoker going back to cigarettes long term and showing a positive impact on certain measures of cardiovascular health." You further indicate that this future guidance also will address potential alternative treatment regimens, such as "pre-treatment before quit day," quitting by gradual reduction (reduce-to quit), or using two NRT drug products together.

The exploration of new clinically relevant outcomes for smoking cessation products has great potential to support new indications for existing products, as well as encouraging companies to develop new cessation products that can be shown to effectively achieve those outcomes and thereby increase the likelihood of eventual cessation. Moreover, we believe the existing body of scientific knowledge supports alternative treatment regimens that are safe and effective (particularly if continued smoking is genuinely weighed in the benefit-risk analysis), but that are not reflected in the current labeling of NRTs and other cessation products currently on the market.

We believe there is a broad consensus that strong, well-documented, peer-reviewed evidence exists to support the following changes in labeling and indications:

- (1) Combination use. The U.S. Public Health Service Clinical Practice Guidelines (PHS Guidelines), issued in 2008, found strong scientific support that some smokers derive substantial benefit from the combination use of a nicotine patch and a more rapid-delivery form of NRT, such as gum or spray, as compared to use of one NRT alone. Experts testifying at the January 26, 2018 meeting of FDA’s Nicotine Steering Committee agreed. There also is evidence that combining NRT and bupropion is more effective than bupropion alone. And there is little evidence that combination use increases the risk of dependence or is otherwise unsafe.
- (2) Longer-term use. Many smokers who try to quit are unable to do so within the use period currently on the label for smoking cessation products. According to the PHS Guidelines, however, long-term NRT use is safe and effective for smoking cessation. Evidence supporting this conclusion also was presented at the January 26, 2018 meeting and in other written comments filed in the related docket.
- (3) Pre-quit NRT use in “reduce to quit” regimen. At the January 26 meeting, the Steering Committee heard testimony that a “reduce to quit” regimen with NRT is more effective than placebo and results in quit rates comparable to abrupt cessation.

We believe that if these changes were made, it would make a measurable difference in the number of people who would successfully stop using combusted tobacco products.

Changes in Labeling and Indications Are Only Part of the Solution: It Is Essential That CDER Explore and Adopt Regulatory and Organizational Changes To Create An Environment in Which Manufacturers Will Invest in the Development of New Smoking Cessation Products.

- (1) FDA Should Take Affirmative Steps to Explore Alternatives to Long-Term Clinical Trials for Promising New Products or for New Indications for Existing Products, Where Sufficient Evidence is Available to Meet Both the Safety and Efficacy Without Long Term Clinical Trials

For particularly promising new products and indications, and without weakening the standards for safety and effectiveness, FDA can broaden the kind and scope of scientific evidence that may support claims of safety and effectiveness beyond long-term clinical trials. There is a wealth of data about the effects of nicotine delivery, both from decades of use in the U.S as well as from the widespread use of nicotine delivery products in various forms all over the globe. FDA should create a docket to solicit the best available scientific evidence, including convening leading experts, to determine whether there is sufficient support for the use of alternative data and methods to assess safety and effectiveness for cessation products that would allow for shorter-term and less expensive clinical trials. This could include the use of existing clinical data, epidemiological data, and other real-world data without compromising FDA’s safety and efficacy standards.

Based upon the existing global experience with products that deliver nicotine and the peer review published literature, we believe evidence criteria can be developed that reduces costs and expedites the review process without compromising or creating an exception to FDA’s existing standards

(2) FDA Should Establish Criteria for Use of Accelerated Pathways to Approval for Promising Smoking Cessation Drugs.

One of the barriers to innovation in smoking cessation products is the amount of time required to pursue NDAs or SNDAs. That problem has become even more consequential in light of the fast-changing nature of the nicotine product market in the past few years. Given the continuing epidemic of smoking, and related disease and mortality, and the relative paucity of effective, widely used therapeutic treatments, smoking cessation products should be leading candidates for accelerated approval and priority review. Indeed, Congress agreed, directing FDA to consider treating cessation products as fast track research and approval products at an applicant's request. See 21 U.S.C. 387r.

FDA should lay the groundwork for fast track treatment of a cessation therapy, to give potential applicants a clear understanding of the standards and to highlight the benefits that accompany such priority review. To do so, FDA should collect the best available evidence and set forth clear, specific criteria for eligibility of specified types of products for fast track treatment and/or as breakthrough therapies and should clearly delineate the showing needed for a smoking cessation product to receive such treatment.

(3) FDA Should Evaluate Whether To Modify Its Current Organizational Structure To Create a New Environment of Innovation To Confront the Epidemic of Smoking-Related Disease.

Having observed FDA's treatment of smoking cessation products over many years, we believe it is time for the agency to consider organizational changes that will better facilitate the development of new and innovative products that satisfy the standards of safety and effectiveness. It appears to those of us outside the agency that the consideration of smoking cessation products has not reflected the risk/benefit ratio of assisting smokers to quit an addiction that will kill 50% of all long term users.

FDA should consider a number of possible organizational changes that signal to manufacturers of promising smoking cessation products that FDA is "open for business" and ready to work collaboratively with applicants to get products to approval. Such changes could include moving evaluation of smoking cessation products from CDER's Division of Anesthesia, Analgesia, and Addiction (DAAAP) to another office within CDER with experience evaluating treatments for the diseases caused by smoking (e.g., the Office of Hematology and Oncology Products). The agency should also consider creating one or more positions of leadership within the reviewing division or office with dedicated focus on and responsibility over smoking cessation products. Such a leader could expedite reforms needed to make the CDER pathway more efficient and effective in encouraging innovation. Given the importance of close coordination between CDER and CTP, the agency should also look for ways to directly involve CTP personnel in the drug approval process, to bring CTPs expertise in tobacco-related disease to bear on the review and approval of applications for smoking cessation drugs.

Conclusion

In your August 3 statement, you described FDA's work on medicinal smoking cessation products as "aimed at creating a more flexible framework that enables the development of safe and effective product innovations that have the potential to be helpful in assisting smokers quit

combustible cigarettes and improve their health.” We fully endorse that goal and appreciate the initial steps FDA is taking toward achieving it.

We believe the time for creative and decisive action has come to implement the agenda we have described in this letter. As we stated at the outset, we would appreciate the opportunity to meet with you and your senior staff at CDER and CTP to explore these issues in greater detail. The contact person for this request is: Dennis Henigan, Vice President for Legal and Regulatory Affairs, Campaign for Tobacco-Free Kids, dhenigan@tobaccofreekids.org.

Sincerely,

American Academy of Pediatrics

American College of Cardiology

American Lung Association

Association for the Treatment of Tobacco Use and Dependence (ATTUD)

Campaign for Tobacco-Free Kids

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