

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,

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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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