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PUBLIC HEALTH
LAW CENTER
at Mitchell Hamline School of Law



April 23, 2019

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

Re: Docket No. FDA-2019-D-0297, Draft Guidance, “Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products: Guidance for Industry” (Feb. 2019).

Dear Sir or Madam:

The undersigned organizations, committed to protecting and promoting the public health by reducing the use of tobacco products, respectfully submit comments on the draft guidance, “Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products: Guidance for Industry (Feb. 2019) (“Draft Guidance”).¹ The Draft Guidance is intended “to assist sponsors in the clinical development of nicotine replacement therapy (NRT) drug products, including but not limited to those intended to help cigarette smokers stop smoking.” Draft Guidance at 1. As discussed in more detail below, we are concerned that the Draft Guidance fails to adequately address the barriers to innovation in smoking cessation products and fails to adopt measures that would encourage more widespread use of NRTs that are proven to help people quit cigarette smoking.

We urge FDA to undertake a broader review of the need for more innovative smoking cessation products and not confine its analysis to existing approved NRT drug products. The fact is that existing market incentives favor companies who are marketing nicotine products, like e-cigarettes, as recreational products, with substantial disincentives for companies to devote their resources to satisfying the safety and effectiveness standards for drug approval under the Federal Food, Drug and Cosmetic Act (FD&C Act). This calls for an agency-wide approach to smoking cessation designed to make the drug approval pathway more viable for responsible companies seeking to develop products that can be scientifically shown to help smokers quit, while imposing rational regulation on the recreational nicotine market to end the current epidemic of youth e-cigarette usage and ensure that all e-cigarettes on the market (or seeking entry into the

¹ See 84 Fed. Reg. 5693 (February 22, 2019).

market) meet the public health standard of the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act or TCA).

A. Background

As FDA has previously noted, upwards of 480,000 premature deaths are caused by cigarette smoking every year. Cigarette smoking remains the leading preventable cause of death in the U.S. In August 2018, Commissioner Gottlieb 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.” Indeed, in the TCA, Congress found that “[t]obacco dependence is a chronic disease, one that typically requires repeated interventions to achieve long-term or permanent abstinence.” TCA § 2(33). Congress declared that a purpose of the law was “to promote cessation to reduce disease risk.” *Id.* § 3(a). To that end, Congress enacted section 918 of the FD&C Act, which specifically directed FDA to look for ways to expand the reach of NRTs. Under section 918, FDA must:

- (1) at the request of the applicant, consider designating products for smoking cessation, including nicotine replacement products, as fast track research and approval products within the meaning of section 506;
- (2) consider approving the extended use of nicotine replacement products (such as nicotine patches, nicotine gum, and nicotine lozenges) for the treatment of tobacco dependence; and
- (3) review and consider the evidence for additional indications for nicotine replacement products, such as for craving relief or relapse prevention.

21 U.S.C. 387r(a).² As indicated below, we do not believe the Draft Guidance goes far enough toward a new regulatory approach that would lead to more widespread and effective use of NRTs and other cessation products, consistent with congressional intent as set forth in section 918.

B. There Is Substantial Evidence that Long-Term NRT Use and Use of Multiple NRTs in Combination Is Safe and Can Be More Effective Than the Use Regimen in Current NRT Labeling.

As Commissioner Gottlieb noted in August 2018, most of the existing NRTs were approved more than twenty years ago. He 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.”³ In fact, there is a

² While the FD&C Act refers to “craving relief” as an indication, the Draft Guidance treats it as a “secondary endpoint” that after a successful clinical efficacy trial, may be added to the labeling of an NRT that already has approval for one of two other uses—“smoking cessation” or “reduction in risk of relapse.” Draft Guidance at 8.

³ Moreover, as to non-nicotine medicines, the pace of innovation also has been slow, with no new medications approved in the last ten years. Steps to encourage innovation should address not only NRTs, but other non-nicotine cessation products as well.

broad consensus that strong, peer-reviewed evidence already exists to support certain changes in labeling and indications of NRTs that could lead to expanded use of NRTs.

For example, in 2008—11 years ago—the U.S. Public Health Service issued Clinical Practice Guidelines (PHS Guidelines) that found strong scientific support for a finding 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. And there is little evidence that combination use increases the risk of dependence or is otherwise unsafe.⁴ The PHS Guidelines also found that many smokers who try to quit are unable to do so within the use period currently on the label for smoking cessation products, but that longer-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.⁵ The evidence strongly supports a labeling change that would encourage smokers to use NRTs for a longer period than the current label instructions, and FDA should outline how publicly available research findings might be submitted as part of sponsor-requested labeling changes.

Notwithstanding the PHS’s evidence-based conclusions supporting these use regimens, the Draft Guidance suggests that a maker of one of the NRTs covered by the PHS Guidelines will have to perform an actual-use efficacy trial to add alternative regimens for OTC use, *id.* at 14,⁶ and a “randomized, double-blind, double-dummy factorial design” clinical studies to establish effectiveness of a particular combination use. *Id.* at 13. Similarly, the Draft Guidance directs any sponsor of an NRT product to perform substantial clinical and other testing before FDA will allow the sponsor to add “secondary endpoints” or use regimens to the product labeling. Although randomized controlled trials are the gold standard, in light of the existing evidence, and the directive contained within the 21st Century Cures Act to enhance the use of real-world evidence, we urge FDA to consider how it might make use of existing data, and permit alternative study designs, to allow NRT sponsors to efficiently align their labels with the scientific evidence supporting expanded NRT use. That is particularly the case for approved NRTs and new NRTs that share characteristics of already-approved products.

Moreover, it is essential that any Final Guidance make it clear that, when assessing 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. Providing greater flexibility to NRT sponsors in how they can satisfy the high standards of the F,D&C Act, and using continued smoking as the relevant comparator would help expand the use of these effective medications and make a measurable difference in the number of people who successfully stop smoking.

⁴ There also is evidence that combining NRT and bupropion is more effective than bupropion alone.

⁵ At the January 26 meeting, the Steering Committee also heard testimony that a “reduce to quit” regimen with NRT is more effective than placebo and results in quit rates comparable to abrupt cessation.

⁶ The Draft Guidance indicates that 5-6 studies—including actual-use/real-world efficacy trials, label comprehension studies and human factor studies—may be necessary to obtain approval for OTC use.

C. FDA Should Strongly Support the Use of Expedited Approval Pathways for Review of NRTs

The Draft Guidance acknowledges that tobacco dependence is a serious or life-threatening condition, one of multiple qualifying conditions to access expedited approval pathways at FDA, but does not send a strong signal that the agency is encouraging NRT sponsors to pursue these pathways or that FDA is committed to looking for opportunities to use those available mechanisms in ways that will result in expanded labeling and use of NRTs.

FDA has historically taken extraordinary measures to respond to public health epidemics—HIV/AIDS, etc.—and Congress created expedited approval pathways to encourage drug makers to invest in development of new therapies. Given the scale and scope of disease caused by tobacco use, FDA should more aggressively communicate that the expedited pathways are “open for business” and that FDA will work with NRT sponsors to limit the time and investment necessary to obtain approval for “secondary endpoints” and new use regimens.

D. Guidance for NRT Development Will Be Most Effective in the Context of an Agency-Wide Approach to Regulation of Nicotine.

The action of Commissioner Gottlieb in creating a Nicotine Steering Committee, composed of representatives of the Center for Drug Evaluation and Research (CDER), the Center for Tobacco Products (CTP) and the Commissioner’s Office, was a recognition of the need for an agency-wide approach to nicotine policy. The need for a comprehensive, coherent approach to nicotine regulation grows with each passing day. With most of the existing NRTs approved more than twenty years ago and with no new non-nicotine smoking cessation medicines approved in the last ten years, innovation in “safe and effective” cessation therapies has been non-existent for far too long. At the same time, we have seen an explosion of recreational nicotine products causing a public health crisis of e-cigarette use and resulting nicotine addiction among our youth.

In addition to being inadequate to furnish sufficient new incentives for innovation in NRT development, usage and labeling, the Draft Guidance represents an overly narrow and inadequate response to the broader misalignment of incentives which is both discouraging development of medicines that help smokers quit and encouraging the continued development and marketing of recreational nicotine products with profoundly adverse public health consequences. We urge FDA to take stronger action, both to help smokers quit and to impose rational controls on recreational nicotine products in the interest of public health

E. FDA Should Encourage the Development of Cessation Therapies in Pediatric Populations

As FDA acknowledges, 90 percent of adult daily smokers started smoking before they turned 18. This fact makes it essential to ensure that tobacco cessation products are effective for and available to the adolescent population. Unfortunately, however, there is a significant gap in the availability of cessation products with labeling for use in pediatric populations. While the Draft Guidance explains the legal requirements and incentives for pediatric studies under the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA), FDA should go further and encourage sponsors of tobacco cessation products to develop them for and study them in pediatric populations. Research to date has shown that NRTs have different effects on adolescents compared to adults. It is therefore imperative that sponsors, when

appropriate, develop pediatric plans as early as possible in the drug development process so that well-constructed research is conducted in adolescents and that adolescent needs are taken into account when designing product characteristics. FDA should also acknowledge that existing evidence suggests that pharmacotherapies for adolescent tobacco use are likely to be most effective when combined with behavioral counseling.

Thank you for your consideration of our comments on the Draft Guidance.

Respectfully submitted,

American Academy of Pediatrics

American Cancer Society Cancer Action Network

American Heart Association

American Lung Association

Campaign for Tobacco-Free Kids

Public Health Law Center

Truth Initiative