



American Academy
of Pediatrics



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

Re: Docket No. FDA-2017-N-6529, "FDA's Approach to Evaluating Nicotine Replacement Therapies"

The Campaign for Tobacco-Free Kids and the American Academy of Pediatrics submit these comments to the above-referenced docket, established in connection with the public hearing held on January 26, 2018.¹

Introduction

It is time for a significant review of the context and manner in which the Food and Drug Administration's Center for Drug Evaluation and Research (CDER) addresses the entire issue of tobacco cessation and its role in curtailing the number of Americans who die from tobacco use. We commend Commissioner Gottlieb's appointment of a Nicotine Steering Committee (Steering Committee) to address this and other issues, as well as the agency's convening of the January 26 meeting of that Committee to consider FDA's approach to evaluating the safety and efficacy of nicotine replacement therapy (NRT) products, as important first steps toward that review.

As a nation we have not appreciated the dire need for high quality products that can help America's 38 million current smokers quit. The urgency of this problem is highlighted by the 500,000 avoidable deaths from tobacco-related disease that occur every year.² Tobacco should be treated as a public health emergency.

In the last 50 years, FDA has approved only nicotine replacement therapy, bupropion and varenicline as safe and effective in doing the one thing that can prevent tobacco-related deaths: help people quit. It has approved no new smoking cessation products in the last decade. While each new approved smoking cessation product has made it possible for more

¹ "The Food and Drug Administration's Approach to Evaluating Nicotine Replacement Therapies; Public Hearing; Request for Comments," 82 Fed. Reg. 56759 (November 30, 2017).

² CDC, "Current Cigarette Smoking Among Adults—United States, 2016," *Morbidity & Mortality Weekly Report*, 67(2):53-59, January 19, 2018. <https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6702a1-H.pdf>; HHS, *The Health Consequences of Smoking – 50 Years of Progress: A Report of the Surgeon General*, (2014).

people to quit, only one-third of all smokers who try to quit use any of these medications and each treatment is successful for only 17 to 33% of the individuals who use it.³

This is a unique time in our history for several reasons:

- Commissioner Gottlieb has made a bold new proposal to drive down the number of people who die from tobacco use by reducing the level of nicotine in cigarettes (and hopefully other combusted tobacco products) to minimally addictive levels.
- Prior to 2009, CDER was the only FDA Center with authority over nicotine. Today, FDA has authority over all nicotine-based products and, therefore, the ability to develop a comprehensive, coherent policy across Centers with a single goal – reduce, to the maximum extent possible, the number of people who die from tobacco use.
- E-cigarette products that deliver nicotine in widely varying quantities (including quantities far higher than permitted in any product authorized by FDA) now are widely available to any purchaser for any purpose. In effect, the ruling in *Sottera, Inc. v. FDA*⁴ turned our regulatory system upside down. The only products subject to rigorous regulation are those that are proven to help people quit. The products that are widely used by youth, and pose a higher abuse potential, face no such restraints. Yet, the new e-cigarette products have a public health value only if they are marketed to addicted smokers who can't quit and they enable them to quit using tobacco products altogether, or to switch completely to less hazardous products, never losing sight that the ultimate goal is quitting all tobacco products. It is time to change that equation.

How many lives could be saved if FDA prioritized the development and wide use of effective products to help people break their addiction to tobacco products? This should be CDER's challenge.

- This requires CDER to be bold and proactive. CDER should convene meetings of manufacturers and innovators of all types in an effort to work out a plan to (1) promote innovation of products with the most promise of helping smokers quit all tobacco products and (2) develop regulatory mechanisms that would allow for speedy review and approval of those products without lowering safety standards.
- FDA should coordinate between CDER and CTP to develop a unified approach that gives top priority to cessation, not harm reduction. While it is true that as Commissioner Gottlieb proposed, there is a role for products that pose minimal risk

³ 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. DOI: <http://dx.doi.org/10.15585/mmwr.mm6552a1>.
Siu, AL, "Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement," *Annals of Internal Medicine* 163(8):622-34, October 20, 2015. Fiore, MC, et al, *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*, Rockville, MD: U.S. Department of Health and Human Services, May 2008.

⁴ *Sottera, Inc. v. FDA*, 627 F.3d 891 (D.C. Cir. 2010).

but enable smokers who can't quit immediately to switch completely, facilitating cessation should be the priority and complete switching should be seen as part of strategy whose goal is to enable every tobacco user to quit altogether.

I. The Public Health Imperative for Innovative Approaches to Smoking Cessation

Although great strides have been made in adopting policies to reduce smoking among children and adults over the last several decades, smoking remains the leading preventable cause of death in America, claiming over 480,000 lives every year.⁵ Life expectancy among smokers is at least 10 years shorter compared to non-smokers.⁶ Currently, more than 16 million people in the United States suffer from smoking-cause disease, including lung cancer, emphysema and heart disease.⁷

Despite the known risks of smoking and demonstrable benefits of quitting, far too few smokers are able to quit successfully. In 2015, 68 percent of smokers reported that they want to quit and 55.4 percent of all smokers made a quit attempt that year, but only 7.4 percent had quit within that year.⁸ Though studies continue to show higher success in quitting among those who use some form of approved medication,⁹ only one-third of smokers use any of those medications when making a quit attempt.¹⁰ Unfortunately, even when cessation medications are used, quit rates are less than optimal, roughly 17 to 33 percent.¹¹ The need for more effective smoking cessation therapies is readily apparent.

Between 1984 and 2006, FDA approved New Drug Applications (NDA's) for the nicotine patch, gum, lozenge, spray and inhaler, along with two non-nicotine based therapies, bupropion

⁵ U.S. Dept. of Health and Human Services (HHS), *The Health Consequences of Smoking – 50 Years of Progress: A Report of the Surgeon General*, (2014) 17 (Executive Summary).

⁶ HHS, *The Health Consequences of Smoking – 50 Years of Progress: A Report of the Surgeon General*, (2014); Jha, P, et al., “21st Century Hazards of Smoking and Benefits of Cessation in the United States,” *New England Journal of Medicine* 368(4):341–50, 2013. U.S. Centers for Disease Control and Prevention (CDC), “Tobacco-Related Mortality,” Smoking & Tobacco Use Fact Sheet, accessed January 23, 2018, http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm.

⁷ CDC, “Fast Facts,” Smoking & Tobacco Use Fact Sheet, accessed January 23, 2018, http://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm#toll.

⁸ 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. DOI: <http://dx.doi.org/10.15585/mmwr.mm6552a1>.

⁹ Siu, AL, “Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement,” *Annals of Internal Medicine* 163(8):622-34, October 20, 2015. Cahill, K, et al., “Pharmacological interventions for smoking cessation: an overview and network meta-analysis,” *Cochrane Database of Systematic Reviews* 4:CD009329, 2013.

¹⁰ 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. DOI: <http://dx.doi.org/10.15585/mmwr.mm6552a1>

¹¹ Siu, AL, “Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement,” *Annals of Internal Medicine* 163(8):622-34, October 20, 2015. Fiore, MC, et al, *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*, Rockville, MD: U.S. Department of Health and Human Services, May 2008.

(ZYBAN and generics) and varenicline (CHANTIX).¹² In recent years, there has been little development and approval of innovative, new smoking cessation products.

The need to spur the development of smoking cessation products was recognized by Congress when it enacted the Family Smoking Prevention and Tobacco Control Act in 2009 (Tobacco Control Act). Section 918 directed FDA to issue a report, within three years, examining “how best to regulate, promote and encourage the development of innovative products and treatments,” but significant change did not occur.

Through Citizen Petitions and other communications with FDA, the public health community has regularly called on FDA to review its approach to smoking cessation products to remove barriers to the use of approved products and to foster the development of innovative products.¹³

II. The New Market Reality for Nicotine Products

In 2010, the U.S. Court of Appeals for the D.C. Circuit held in the *Sottera* case that, under the recently-enacted Tobacco Control Act, all products made or derived from tobacco and intended for human consumption must be regulated as tobacco products if customarily marketed, but are regulated under the drug/device provisions of the Food, Drug and Cosmetic Act if “marketed for therapeutic purposes.”¹⁴

The combination of the *Sottera* ruling and FDA’s lengthy delay in exercising its regulatory authority over e-cigarettes as tobacco products led to the emergence of an uncontrolled, unregulated market in highly-addictive e-cigarettes, giving rise to a host of risks to public health. For example, the January 23, 2018 National Academy of Sciences, Engineering and Medicine Report (NASEM Report) found there is “substantial evidence” that e-cigarette use increases the risk of ever using combustible tobacco cigarettes among youth and young adults.¹⁵

In addition, the NASEM Report found there is only limited evidence that e-cigarettes “may be effective aids to promote smoking cessation” and while there are some observational studies that more frequent use of e-cigarettes is associated with increased likelihood of cessation, the Report found there is “insufficient evidence from randomized controlled trials about the effectiveness of e-cigarettes as cessation aids compared with no treatment or to Food and Drug Administration–approved smoking cessation treatments.”

¹² Department of Health and Human Services, *Report to Congress: Innovative Products and Treatments to Achieve Abstinence from Tobacco Use, Reductions in Consumption of Tobacco, and Reductions in the Harm Associated with Continued Tobacco Use*, Required by Section 918 of the Federal Food, Drug and Cosmetic Act, April 22, 2013 ,

¹³ See generally, FDA Combined Response to Three Citizen Petitions (April 1, 2013); Written comments of Campaign for Tobacco-Free Kids in Docket No. FDA-2012-N-1148 (January 16, 2013).

¹⁴ *Sottera, Inc. v. FDA*, 627 F.3d 891 (D.C. Cir. 2010).

¹⁵ National Academy of Sciences, Engineering and Medicine, *Consensus Study Report, Public Health Consequences of E-Cigarettes, Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems*, January 23, 2018.

Yet, today, manufacturers who want to market products to help smokers quit and who want to promote them to adult smokers, face a regulatory system that has discouraged innovation. By contrast, manufacturers who market products that deliver nicotine through inhalation in varying quantities and flavors without regard to whether they will help smokers quit or whether they appeal to kids, face a far easier regulatory environment. Without sufficient regulation, nearly a decade after e-cigarettes exploded on the market, we have not yet developed sound scientific evidence establishing which, if any, of these products may be helpful for cessation.

III. The Need for an FDA-Wide Reevaluation of Policy Toward Nicotine and Smoking Cessation Products

In light of the continuing devastating toll of smoking-related disease, and the widespread availability of nicotine products to the general public, it is urgent for FDA to engage in an agency-wide reevaluation of its regulatory approach to smoking cessation products and nicotine-delivery products.

A. In Evaluating Possible New Indications or Labeling Changes for Existing Products and Possible Barriers to the Development of New Products, FDA's Risk/Benefit Calculus Must Be Based on Continued Smoking as the Relevant Comparator

In evaluating its approach to the development of products that are effective in breaking the hold of tobacco addiction, FDA should recognize that the continued cost of the status quo – that is, the continued use of a product that kills half of its users¹⁶ – is the critical comparator. The safety of new, innovative cessation therapies should be determined relative to continued cigarette smoking. With more than 38 million current smokers, the introduction of new, more effective cessation products, and the authorization of now-unauthorized uses of existing products, could potentially save tens of thousands, if not hundreds of thousands, of lives every year.¹⁷

FDA has widespread experience with NRT over more than two decades. It is true that there has been less experience with products that deliver nicotine through inhalation and that many such inhalation products may present different issues of abuse potential and lung damage. But the reality FDA today faces is that nicotine is being delivered through inhalation to huge numbers of users. Regulation that redirects those users to products FDA has determined help smokers quit, will both lower that abuse potential and increase beneficial public health outcomes.

This does not require FDA to lower its scientific or safety standards. FDA possesses both the regulatory authority and regulatory flexibility to evaluate the conditions of the use of existing products, enable changes to existing drugs and promote the development of more effective products, as described further below.

¹⁶ HHS, *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*, 2014, <http://www.surgeongeneral.gov/library/reports/50-years-of-progress/>.

¹⁷ CDC, “Current Cigarette Smoking Among Adults—United States, 2016,” *Morbidity & Mortality Weekly Report*, 67(2):53-59, January 19, 2018. <https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6702a1-H.pdf>

B. CDER Should Evaluate Whether Indications and Labeling for Existing Approved Smoking Cessation Products Should Be Revised to Encourage Greater Consumer Acceptance and Use of Those Products

As noted above, although most smokers want to quit, relatively few of them take advantage of existing cessation medicines and among those that do, their success rate is still relatively low. The limitations of existing NRT products, and the way these products are marketed, slow our progress toward ending tobacco-related disease.

CDER needs to analyze whether various use restrictions, and aspects of current labeling on NRTs and other cessation products, may be discouraging successful use of existing treatments, and whether more can be done to increase the number of people who use these products properly. In response to various Citizen Petitions, and information submitted to FDA in connection with a hearing convened by the agency in November, 2012,¹⁸ CDER did find sufficient evidence to recommend some minor modifications to certain warnings and directions for use relating to the use of OTC NRT concomitantly with cigarettes or with other nicotine-containing products (including other NRTs) and relating to the use of OTC NRT for longer than the labeled period of treatment.¹⁹ However, these are modest labeling changes and FDA took no action toward approving new indications. There continues to be a need for FDA to evaluate other potential labeling changes and possible new indications.

A number of ideas for new indications for existing products, and further labeling changes, advanced at the January 26 hearing and elsewhere, deserve serious consideration by FDA:

- Longer-term use of NRTs. None of the FDA-approved NRT products are approved for long-term use. However, many smokers who try to quit are unable to do so within the length of time approved for smoking cessation products. According to the U.S. Public Health Service Clinical Practice Guidelines, long-term NRT is effective for smoking cessation.²⁰ Experts testifying at the January 26, 2018 hearing agreed.²¹ The current labeling of NRTs fails to indicate that long-term use of NRTs may be effective.
- Combination NRT medications. The PHS Clinical Practice Guidelines discuss a number of studies showing that some patients benefit from the combined use of smoking cessation products, including different NRT products,²² as noted in the January 26, 2018 hearing²³ and in other written comments to this docket.²⁴ Nothing in the current labeling of NRTs suggests the effectiveness of certain

¹⁸ See e.g. Comments of Campaign for Tobacco-Free Kids in Docket No. FDA-2012-N-1148 (January 16, 2013).

¹⁹ Modifications to Labeling of Nicotine Replacement Therapy Products for Over-the-Counter Human Use, 78 Fed. Reg. 19718 (April 2, 2013). See also, Report to Congress 16; FDA Response to Citizen Petitions (April 1, 2013) 5.

²⁰ Fiore, MC, et al., *Treating Tobacco Use and Dependence: 2008 Update*, U.S. Public Health Service Clinical Practice Guidelines, May 2008 (PHS Clinical Practice Guidelines).

²¹ See e.g. Dr. Dorothy Hatsukami, Comments on Nicotine Replacement Therapies from the American Association for Cancer Research (January 26, 2018) (Hatsukami), Slide #10.

²² PHS Clinical Practice Guidelines, at 120.

²³ Hatsukami, Slide #8.

²⁴ Written comments in Docket No. FDA-2017-N-6529 submitted by the Association for the Treatment of Tobacco Use and Dependence (February 15, 2018) (ATTUD written comments).

combinations of NRTs or combinations of NRTs and other FDA-approved cessation products like bupropion or varenicline.

- Pre-quit NRT use in “reduce to quit” regimen. At the January 26 hearing, 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.²⁵ Yet nothing in the current labeling of NRTs indicates the effectiveness of a properly conducted reduce to quit strategy.
- Labeling changes to better communicate that NRTs are far safer than continued smoking. The Committee heard testimony that use of NRTs is discouraged by existing warning labels that do not sufficiently communicate that NRTs are substantially less harmful to health than continued cigarette smoking. Studies reveal significant misperceptions or lack of knowledge, among smokers and healthcare providers, about the harm of nicotine and NRTs.²⁶ Warnings could be revised to provide smokers with well-established facts about the dangers of smoking compared to the comparatively low risks of side effects from NRTs.²⁷

C. FDA Should Consider Policies to Drive Innovation in the Development of New Smoking Cessation Products

CDER must no longer be a passive participant in this process. CDER should proactively reach out to industry to open a forum to foster innovation in the development of smoking cessation products, agree upon what evidence a manufacturer will need to gain approval, discuss how post-market surveillance can contribute to faster approvals with better outcomes and discuss how unnecessary barriers can be removed without compromising safety standards.

For example, CDER should jointly explore with industry whether the effectiveness of existing NRTs would be enhanced by the ability to safely deliver to smokers higher doses of nicotine more rapidly to the brain. Such NRTs could be effective in reducing cravings and withdrawal symptoms. Such an innovation may be especially important in light of evidence that cigarettes have become more addictive over the last 15 years.²⁸

D. FDA Should Implement Procedures for Fast Track and Other Accelerated Approval Authorities to Facilitate Approval of New and Effective Treatments

FDA has available to it fast track and other accelerated approval procedures that can be used to address serious and life-threatening conditions for products that can potentially fill an “unmet medical need.” Section 918 of the Food, Drug and Cosmetic Act, as amended by the Tobacco Control Act, directed FDA to consider the designation of smoking cessation products as fast track products. CDER should evaluate how those standards should be adapted and applied specifically to smoking cessation products. The evaluation of approval procedures by CDER should be carefully coordinated with CTP.

²⁵ Hatsukami, Slide #11.

²⁶ Hatsukam, Slide #12.

²⁷ ATTUD written comments.

²⁸ ATTUD written comments.

Conclusion

The Steering Committee has a unique opportunity. If it acts boldly, it has the opportunity to greatly accelerate the pace at which we reduce the death and disease caused by tobacco use. CDER has an essential role, but this change will not come about through business as usual. It will come about only if FDA has one unified, coordinated policy that cuts across the agency, with its top priorities being to drive down the use of those products that kill and make sure every tobacco user is provided the best possible assistance in quitting all tobacco products.

Campaign for Tobacco-Free Kids

American Academy of Pediatrics