

February 15, 2018

Dockets Management Staff (HFA-305)  
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

To Whom It May Concern:

The American Association for Cancer Research (AACR), with over 40,000 members, is the oldest 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) Approach on Evaluating Nicotine Replacement Therapies (NRTs).

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 one in ten deaths. Additionally, 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. Most people who use tobacco regularly do so because they are addicted to nicotine, the major addictive component in tobacco. Although most users express a desire to reduce their use or stop entirely, overcoming the addiction is difficult and may require both pharmacologic and behavioral treatments, as well as policy changes.

One of the mechanisms tobacco users rely on to overcome their addiction is NRTs. Unfortunately, there has been little innovation in NRT products over the past two decades. These products are often unappealing to many users and indications for use do not allow for personalizing treatments to make them more desirable and effective. The AACR applauds the

FDA for placing nicotine addiction at the center of the Agency's tobacco regulation efforts and for encouraging innovation in NRT products. We thank the Agency for taking this important step forward in improving public health and reducing the incidence of disease.

In response to the FDA's Federal Register announcement, the AACR provides the following comments:

1. *Might there be ways to improve upon the currently available delivery systems to yield new over the counter (OTC) NRT products that might be more effective? If so, what evidence would be needed to support such changes, and how should they be evaluated?*

**The AACR advocates for improving the appeal and nicotine delivery of NRTs:**

Current uneven playing field. In the 1998 Food and Drug Law monograph, Slade, Henningfield, and Warner indicated that the regulatory field for tobacco and NRT products is uneven. That is, NRTs, which are the least harmful nicotine-containing products, have had to undergo the most rigorous testing and restrictive regulations. On the other hand, at that time, minimal manufacturing regulations were imposed on the most harmful product, cigarettes. Cigarettes and smokeless tobacco could be manufactured to be highly addictive and toxic, whereas NRTs were manufactured to be less appealing and to result in low abuse liability for fear that tobacco naïve users might initiate use or consumers would become addicted to the product. These restrictions have led to medications that do not engender the most optimal uptake, sustained use, and effectiveness in smokers. More recently, products that have more appeal, such as electronic nicotine delivery systems (ENDS), have had greater uptake among smokers than medicinal products.<sup>1</sup> Based on these observations, the AACR recommends that the FDA consider allowing the manufacture of medicinal products that might have greater success in competing with and substituting for cigarettes. This initiative would mean approving medicinal products that have greater and more rapid delivery of nicotine to the body and more appeal (i.e., delivery systems that are better substitutes for the sensory aspects of smoking).

Evidence to support NRT improvement. The evidence to support improvement of current delivery systems can be inferred from the greater uptake of nicotine products with more

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<sup>1</sup> Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *BMJ*. 2016;354: i4645.

appeal (e.g., ENDS) relative to medicinal nicotine.<sup>2</sup> Epidemiological studies indicate that some smokers successfully quit smoking with daily use of ENDS compared to not using ENDS<sup>3</sup> and clinical trials with ENDS suggest that these products can be efficacious smoking cessation tools.<sup>4</sup>

Recommendations:

- a. Based on the data from ENDS along with research demonstrating that ENDS result in substantially reduced toxicity relative to cigarettes,<sup>5</sup> it is recommended that the FDA find a way to enable investigators to conduct randomized clinical trials to test these devices for smoking cessation. Favorable results might stimulate companies to pursue the development of similar products as smoking cessation aids. Evidence for safety should still be imperative in approving a medication for smoking cessation; however, safety of a product could also be based on cigarettes as the comparator. For example, some chemotherapeutic agents can be very toxic; however, compared to progression of cancer, this toxicity can be tolerated. The same logic should apply to a medication for smoking cessation; that is, compared to continued use of a highly toxic and addictive product, the use of a substantially less toxic, but not completely safe, medication should be considered.
- b. Besides safety, randomized clinical trials should be conducted to determine the uptake and efficacy of novel nicotine delivery systems compared to currently existing medicinal products. This is particularly important because the most effective pharmacological approach to stop smoking is a non-nicotine product (varenicline), so efficacy of novel nicotine delivery systems should be compared with the most effective product to assure that

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<sup>2</sup> Nelson VA, Goniewicz ML, Beard E, et al. Comparison of the characteristics of long-term users of electronic cigarettes versus nicotine replacement therapy: A cross-sectional survey of English ex-smokers and current smokers. *Drug Alcohol Depend.* 2015; 153:300-305.

<sup>3</sup> Glasser AM, Collins L, Pearson JL, et al. Overview of electronic nicotine delivery systems: a systematic review. *Am J Prev Med.* 2017;52(2):e33-e66.

<sup>4</sup> Villanti, A. C., Feirman, S. P., Niaura, R. S., Pearson, J. L., Glasser, A. M., Collins, L. K., and Abrams, D. B. (2018) How do we determine the impact of e-cigarettes on cigarette smoking cessation or reduction? Review and recommendations for answering the research question with scientific rigor. *Addiction*, 113: 391–404. doi: [10.1111/add.14020](https://doi.org/10.1111/add.14020).

<sup>5</sup> National Academies of Sciences, Engineering, and Medicine. 2018. *Public Health Consequences of e-cigarettes*. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24952>.

smokers are appropriately provided that which has the greatest potential to help them stop smoking.

- c. The issue of continued use of a product should be examined, but prolonged use should not be penalized if it prevents relapse to smoking.
  - d. Consumer perception of the product among tobacco naïve individuals should be examined to determine ways to minimize the product's appeal among this population.
2. *Are there additional indications or regimens for OTC NRT products that could be explored? Concepts to consider could include relapse prevention, craving reduction, maintenance, reduce to quit, use of short- and long-acting products in combination, or cessation of non-cigarette tobacco products. What evidence would be needed to support each indication or regimen?*

As with other areas of pharmacological treatments, one size does not fit all individuals. Therefore, greater flexibility and indications of how these products can be used might promote greater uptake and success. Because of the urgency to help millions of smokers to more effectively quit smoking, there should be a mechanism to fast track approval of medicinal nicotine for these indications based on existing supporting science.

**Combination of NRTs:** There is sufficient evidence demonstrating that using a combination of NRT products (long and short-acting NRTs) results in greater smoking cessation success and is safe.<sup>6</sup> Consumers should be informed about the increased efficacy of combination NRT products compared to NRT monotherapy.<sup>7</sup> The efficacy and safety of combining a nicotine patch with a shorter-acting NRT formulation have been described in the Cochrane report<sup>8</sup> and the U.S. Department of Health and Human Services Clinical Practice Guideline for Tobacco Use and Dependence, which designated combination NRT as the most effective treatment option.<sup>9</sup> Moreover, combination NRT is one of two first line medication options (when combined with at least 4 sessions of

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<sup>6</sup> Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2012;11:CD000146.

<sup>7</sup> Piper ME, Smith SS, Schlam TR, et al. A randomized 9;66(11):1253-1262.

<sup>8</sup> Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2012;11:CD000146.

<sup>9</sup> Fiore M, Bailey W, Cohen S, et al. *Treating tobacco use and dependence. Clinical practice guideline.* Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; June 2000.

counseling) in the National Comprehensive Cancer Network (NCCN) Smoking Cessation Guidelines.<sup>10</sup>

- **Long-term use of medicinal nicotine (indications for harm reduction and smoking cessation):**

*Harm reduction:* Although the ultimate goal is to help tobacco users quit use of all nicotine products including NRT, there are some individuals who experience difficulty in doing so. For these individuals, the use of NRT over cigarette smoking is likely to lead to reduced harm to health. Reduction in harm is inferred and supported by Sweden's experience with snus, a low tobacco-specific nitrosamine smokeless tobacco product. Snus use has been associated with lower risk of cancer, cardiovascular disease, and chronic obstructive pulmonary disease compared to cigarette smoking.<sup>11</sup> The substantial uptake of snus and the associated reduction in smoking, particularly among males, has resulted in Sweden experiencing the lowest tobacco-related mortality and morbidity compared to males from other European Union countries.<sup>12</sup> Medicinal nicotine results in significantly lower toxicant exposure than snus;<sup>13</sup> therefore, there is sufficient evidence to support use of NRT for harm reduction. However, consumers should be informed that merely reducing cigarettes smoked by use of NRT is unlikely to result in reduced harm,<sup>14</sup> and reduction to very low levels that might result in potential reduced harm, might be difficult to achieve.

*Smoking cessation:* Several prior studies suggest that short and long-term courses of NRT have equivalent efficacy;<sup>15</sup> however, recent research evidence suggests

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<sup>10</sup> Shields PG, Herbst RS, Arenberg placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Arch Gen Psychiatry*. 200D, et al. Smoking Cessation, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(11):1430-1468.

<sup>11</sup> Stepanov I, Hatsukami D. Call to establish constituent standards for smokeless tobacco products. *Tob Regul Sci*. 2016;2(1):9-30.

<sup>12</sup> Ramstrom L, Wikmans T. Mortality attributable to tobacco among men in Sweden and other European countries: an analysis of data in a WHO report. *Tob Induc Dis*. 2014;12(1):14.

<sup>13</sup> Hatsukami DK, Jensen J, Anderson A, et al. Oral tobacco products: preference and effects among smokers. *Drug Alcohol Depend*. 2011;118(2-3):230-236.

<sup>14</sup> Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2012;11:CD000146.

<sup>15</sup> Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2012;11:CD000146.

that extended duration NRT may increase quit rates and recovery from smoking lapses. For example, several studies have shown that smokers benefit from longer use of the nicotine patch for up to 6 months.<sup>1617</sup> Based on this evidence, it is important to allow for at least 6 months of nicotine patch use, which might be beneficial to some smokers.

- **Reduce to quit:** Not all smokers are ready to quit smoking. In one study, almost half of smokers planning to quit in the next 12 months were interested in gradual reduction of cigarette intake prior to quitting.<sup>18</sup> Several studies have shown that reducing to quit with NRT is more effective than with placebo.<sup>19</sup> Reducing to quit results in comparable quit rates as abrupt cessation,<sup>20</sup> indicating that reduce to quit does not compromise quitting success.

3. *What data would be required to demonstrate health benefits of reduction in consumption of combustible tobacco products?*

Since conducting randomized clinical trials to empirically study the health benefits of reduced combustible tobacco product consumption in an ethically feasible manner may provide insufficient evidence, the AACR recommends that the FDA support a variety of epidemiological and animal studies as multiple types of data can and should be used to make causal inferences in large populations.<sup>21</sup> To assist in the assessment of this type of information the World Health Organization has published guidance for assessing

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<sup>16</sup> Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wileyto EP, Hitsman B. Long-term Nicotine Replacement Therapy A Randomized Clinical Trial. *JAMA Intern Med.* 2015;175(4):504–511. doi:10.1001/jamainternmed.2014.8313

<sup>17</sup> Joseph, A.M., et al., “Chronic Disease Management for Tobacco Dependence,” *Archives of Internal Medicine*, 171(21):1894-1900, 2011.

<sup>18</sup> Shiffman S, Ferguson SG, Strahs KR. Quitting by gradual smoking reduction using nicotine gum: a randomized controlled trial. *Am J Prev Med.* 2009;36(2):96-104 e101.

<sup>19</sup> Fucito LM, Bars MP, Forray A, et al. Addressing the evidence for FDA nicotine replacement therapy label changes: a policy statement of the Association for the Treatment of Tobacco use and Dependence and the Society for Research on Nicotine and Tobacco. *Nicotine Tob Res.* 2014;16(7):909-914.

<sup>20</sup> Lindson N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. *Cochrane Database Syst Rev.* 2010(3):CD008033.

<sup>21</sup> Glass TA, Goodman SN, Hernán MA, Samet JM. Causal Inference in Public Health. *Annual review of public health.* 2013; 34:61-75. doi:10.1146/annurev-publhealth-031811-124606.



epidemiological evidence for environmental health risk.<sup>22</sup> Finally, mortality studies indicate that as much as a 50% reduction in smoking long-term provides no benefit for mortality reduction.<sup>23</sup> Thus, it is unknown how much reduction would be needed to provide a health benefit and whether this level can be sustained. However, completely switching from combustibles to NRT is likely to result in health benefits (see #2).

4. *Are there OTC NRT products that could be studied for use in combination that might result in reduced tobacco related health impacts? What evidence would be needed to support the safety and efficacy of these products when used in combination?*

The AACR recommends use of long- and short-acting OTC NRT for complete substitution for cigarettes (see #2). There is sufficient evidence to support that the combination of OTC NRT (patch plus gum or nicotine lozenge) is more effective in promoting smoking cessation than NRT monotherapies. Combination OTC NRT used long-term is also likely to result in reduced harm compared to continued smoking.<sup>24,25</sup>

5. *Is there other information that could be added to labeling for currently approved or new dosage forms of OTC NRT products that would maximize their ability to be used to support smoking cessation? Please consider the various sections of the Drug Facts labeling, including the Uses, Warnings, and Directions sections.*

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<sup>22</sup>Evaluation and Use of Epidemiological Evidence for Environmental Health Risk Assessment. Copenhagen, World Health Organization Regional Office for Europe, 2000.

<sup>23</sup> Tverdal A, Bjartveit K. Health consequences of reduced daily cigarette consumption. *Tobacco Control*. 2006;15(6):472-480. doi:10.1136/tc.2006.016246.

<sup>24</sup> Fucito LM, Bars MP, Forray A, et al. Addressing the evidence for FDA nicotine replacement therapy label changes: a policy statement of the Association for the Treatment of Tobacco use and Dependence and the Society for Research on Nicotine and Tobacco. *Nicotine Tob Res*. 2014;16(7):909-914.

<sup>25</sup> Piper ME, Smith SS, Schlam TR, et al. A randomized 9;66(11):1253-1262.

The AACR recommends educating consumers to optimize NRT efficacy. Smokers and even health care providers are misinformed about the safety of NRT.<sup>26,27,28,29</sup>

Misperceptions have been associated with reduced uptake and less optimal use of NRT,<sup>30</sup> thereby reducing its efficacy. Correcting the misconceptions on product labels would be important. Not all consumers can read and comprehend long product labels; therefore, simplified labels, such as “medicinal nicotine is less harmful to health than cigarette smoking” should be utilized.

6. *Generally, the labeling of OTC NRT products contains a dosing schedule based on duration of use, and FDA has recommended the labeling on OTC NRT products be modified to include the following: “If you feel you need to use [the NRT product] for a longer period to keep from smoking, talk to your health care provider.” What is the impact of longer term NRT treatment? What is the impact on likelihood of cessation of relapse prevention? What data would support an affirmative recommendation to use approved OTC NRT products for durations that exceed those currently included in the Drug Facts labeling of approved OTC NRT products, or would support a chronic or maintenance drug treatment indication for such products?*

Please see long-term use recommendations (#2).

In conclusion, the AACR commends the FDA on their comprehensive plan that places nicotine addiction at the center of the Agency’s tobacco regulatory efforts. Thank you very much for considering our input on this important issue. These comments are based on careful discussion

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<sup>26</sup> Shiffman S, Ferguson SG, Rohay J, Gitchell JG. Perceived safety and efficacy of nicotine replacement therapies among US smokers and ex-smokers: relationship with use and compliance. *Addiction*. 2008;103(8):1371-1378.

<sup>27</sup> Black A, Beard E, Brown J, Fidler J, West R. Beliefs about the harms of long-term use of nicotine replacement therapy: perceptions of smokers in England. *Addiction*. 2012;107(11):2037-2042.

<sup>28</sup> Ferguson SG, Gitchell JG, Shiffman S, Sembower MA, Rohay JM, Allen J. Providing accurate safety information may increase a smoker's willingness to use nicotine replacement therapy as part of a quit attempt. *Addict Behav*. 2011;36(7):713-716.

<sup>29</sup> Silla K, Beard E, Shahab L. Nicotine replacement therapy use among smokers and ex-smokers: associated attitudes and beliefs: a qualitative study. *BMC Public Health*. 2014; 14:1311.

<sup>30</sup> Shiffman S, Ferguson SG, Rohay J, Gitchell JG. Perceived safety and efficacy of nicotine replacement therapies among US smokers and ex-smokers: relationship with use and compliance. *Addiction*. 2008;103(8):1371-1378.



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](mailto:nicole.boschi@aacr.org).

Sincerely,



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