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Docket No. FDA-2019-N-0994
Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD
20852

RE: Modified Risk Tobacco Product Applications for VLN™ King and VLN™ Menthol King, Combusted, Filtered Cigarettes Submitted by 22nd Century Group Inc. Docket No. FDA-2019-N-0994

To Commissioner Stephen M. Hahn:

I write to you on behalf of the R Street Institute, a Washington-based nonprofit public policy research organization dedicated to free markets and real solutions. Exploring ways that tobacco harm reduction strategies can positively impact the lives of people who use combustible cigarettes has been a major focus of R Street's research since the institute opened its doors five years ago.

Responsible for 480,000 deaths a year, cigarette smoking is the leading cause of preventable death in the United States. While nicotine replacement products are available for those who wish to quit, they are not terribly effective at transitioning smokers to complete cessation: Between 25 and 35 percent of smokers relapse within six months, and successful quit rates at one year are estimated to be between 4 and 25 percent.[1] Reduced-risk products represent a new and likely more attractive alternative for people who are either unsuccessful in quitting with traditional nicotine replacement or who might not otherwise quit smoking.

We hope the modified-risk tobacco application process will work to ensure a more healthful populace, and we predict this will occur in two ways. First, we know that labeling is a primary way in which

[1] Ron Borland et al., "How much unsuccessful quitting activity is going on among adult smokers? Data from the International Tobacco Control Four Country cohort survey," *Addiction,* 107:3 (2012) pp. 673-682. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3909986/.
Gemma MJ Taylor et al., "The effectiveness of varenicline versus nicotine replacement therapy on long-term smoking cessation in primary care: a prospective cohort study of electronic medical records," *International Journal of Epidemiology,* 46:3 (2017) pp. 1948-1957. https://www.ncbi.nlm.nih.gov/pubmed/29040555.
Shu-Hong Zhu et al., "E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys," *BMJ,* 358: j3262 (2017). https://www.ncbi.nlm.nih.gov/pubmed/28747333.

consumers receive health information, and allowing products to carry a modified-risk label will likely encourage smokers to switch to less risky products. Second, the MRTP pathway provides an opportunity to correct common misperceptions about smoking—namely that nicotine is responsible for the diseases and deaths associated with smoking.

However, we write here to urge the Food and Drug Administration to deny XXII Century's application for modified-risk labeling in the very low nicotine content cigarettes with the claims "95% less nicotine," "Helps reduce your nicotine consumption" or ".... greatly reduces your nicotine consumption."

We oppose this application on the basis that modified-risk labels should not apply to nicotine content.

Nicotine is not a salient health risk

We urge the FDA to narrow modified-risk claims to those risks that potentially affect primary health outcomes such as lung or cardiovascular diseases and various cancers. We recognize that nicotine exposure is the driving force of cigarette use, but nicotine is a fairly benign substance whose primary physiological effects are on neurotransmission.[2] Studies examining the potential for nicotine to affect mechanisms that lead to cancer have generally examined these effects under conditions and exposure levels that are not physiologically relevant.[3]

While the development of dependence and subsequent addiction is a concern, there is no evidence that prolonged nicotine use actually confers damage or negative health effects on the brain when properly managed. Indeed, the FDA has recently expanded their recommendations regarding the use of nicotine replacement to include indefinite use if there is a risk of reverting to cigarettes.[4]

Health and Modified-Risk Labels

We believe that product labels clearly acknowledging risk reductions in certain tobacco products compared to combustible cigarettes will benefit public health. Product labels are a primary source of health information for consumers, and this likely extends to products beyond tobacco, such as alcohol, sugar sweetened beverages and food. Health labels and warnings are perhaps the best way to reduce disparities in access to knowledge.

With regard to tobacco products, knowledge of the health risks associated with smoking is higher in countries with more comprehensive health warnings, which affects smoking behavior change and quit

[2] Allison M. Glasser et al., "Overview of Electronic Nicotine Delivery Systems: A Systematic Review," *American Journal of Preventative Medicine,* 52:2 (2017) pp. e33–e66. https://www.ncbi.nlm.nih.gov/pubmed/27914771.

[3] Moon-shong Tang et al., "Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice," Proceedings of the National Academy of Science, 116:43 (2019) pp. 21727-21731. https://www.ncbi.nlm.nih.gov/pubmed/31591243.

[4] Agency for Healthcare Research and Quality, "Clinical Guidelines for Prescribing Pharmacotherapy for Smoking Cessation," accessed February 2020. https://www.ahrq.gov/prevention/guidelines/tobacco/prescrib.html.

attempts.[5] It has been suggested that smokers with negative emotions towards warnings are more likely to attempt to quit.[6]

However, when not carefully considered, health and warning labels carry the risk of confusion as well. Contrary to what nearly 75 percent of Americans already believe,[7] the true risks of smoking are not exposure to nicotine, but exposure to the chemicals, particulate matter and carbon monoxide associated with combustion. Labels that promote reduced nicotine as a "modified risk" are likely to send the message that reduction in exposure to nicotine is as effective as reduction in exposure to the products of combustion in achieving health goals and risk reduction.

Very Low Nicotine and the FDA Pathway

Finally, we recognize that the FDA has set forth proposals to address the addictive potential of combustible cigarettes by lowering nicotine concentrations to "non-addictive" levels. We have opposed this proposed rule in the past on the basis that it will create a black market and usher in a breadth of more dangerous products. It also goes against the spirit of Section 907 of the Family Smoking Prevention and Tobacco Control Act, and such a disruption in manufacturing will be unnecessary if other, reduced-risk products are able to flourish in the market.[8] However, if this is the path the FDA intends to take, we do recognize it is possible this approach may result in less cigarettes consumed and, therefore, improve health outcomes for those who continue to smoke. For this to happen the FDA must recognize that all products must be held to this standard, and that in a real-world setting it is very likely smokers will vacillate between VLN and regular nicotine combustible products.

Starting the process to approve modified-risk tobacco product marketing claims for applicants who meet the strict standards set forth by the FDA is the first step to improving the health of our populace. However, this process must focus on the most pervasive risks associated with tobacco use.

Sincerely,
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[5] David Hammond et al., "Effectiveness of cigarette warning labels in informing smokers about the risks of smoking: findings from the International Tobacco Control (ITC) Four Country Survey," *Tobacco Control,* 15 Suppl. 3 (2016) pp. iii19-25. https://www.ncbi.nlm.nih.gov/pubmed/16754942.

[6] Yoo Jin Cho et al., "Path analysis of warning label effects on negative emotions and quit attempts: A longitudinal study of smokers in Australia, Canada, Mexico, and the US," *Soc Sci Med,* 197 (2018) pp. 226-234. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5758420/.

[7] Erin O'Brien et al., "U.S. adults' addiction and harm beliefs about nicotine and low nicotine cigarettes," *Preventative Medicine*, 96 (2017) pp. 94-100.

[8] 111th United States Congress, "Family Smoking Prevention and Tobacco Control Act," 907 § (2009). https://www.govinfo.gov/content/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf.
Clive Bates and Carrie Wade, "Reducing Nicotine in Cigarettes: Challenges And Opportunities," *R Street Policy Study* No. 115 , October 2017. https://www.rstreet.org/2017/10/24/reducing-nicotine-in-cigarettes-challenges-and-opportunities/.