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Docket No. FDA-2018-N-4162
Caryn Cohen
Office of Science
Center for Tobacco Products
Food and Drug Administration
Document Control Center
Bldg. 71, Rm. G335
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

RE: Modified Risk Tobacco Product Applications: Application for Copenhagen Snuff Fine Cut, a Loose Moist Snuff Tobacco Product Submitted by U.S. Smokeless Tobacco Company LLC. Docket No. FDA-2018-N-4162

To the Tobacco Products Scientific Advisory Committee,

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 research since the institute opened its doors five years ago.

As an addiction researcher at The Scripps Research Institute, I led studies examining neurophysiological changes that occur in the early and late stages of drug use and addiction. The Scripps Research Institute continues to produce groundbreaking insights into potential treatments of addiction, including vaccines that target drugs to prevent entry into the brain; deep brain stimulation that mediates compulsive drug seeking; treatments that target the stress response system that perpetuates the cycle of addiction; and targeted drug delivery that prevents the initiation of addiction. Unfortunately, as is often the case, these treatments are many years away from being available and, for lack of access or efficacy, will not help everyone who may benefit from them. Real-world solutions must be available to mitigate the harms that come from risky behaviors, and they must be palatable to the intended audience.

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 have not been 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 have been estimated at between 4 and 25 percent[1]. Alternative reduced risk products represent a new and likely more attractive alternative for people who are either unsuccessful in quitting using traditional nicotine replacement or who might not otherwise quit smoking.

It is for this reason that we urge the Food and Drug Administration to grant Copenhagen Snuff Fine Cut the status of Modified-Risk Tobacco Product with their following proposed claim "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer".

We support this application because Copenhagen Snuff Fine Cut has been shown to be a less harmful alternative to combustible products and because an MRTP label will benefit public health.

Copenhagen Snuff Fine Cut is a safer alternative to combustible cigarettes

The best available research indicates that smokeless tobacco has lower lung toxicity than combustible cigarettes. Smoking is, by far, the most common way to use nicotine, as well as the most harmful way to use it. Because combustion contributes to at least 90 percent of the more than 7,000 chemicals that are inhaled in smoking traditional cigarettes, smokeless tobacco products have an inherently reduced risk profile, which is reflected in this application [2].

In comparing smokeless tobacco products to combustible cigarettes, smokeless tobacco products are far more favorable. As expected, switching from combustible cigarettes results in lower levels of carbon monoxide – an 86 percent decrease compared to combustible cigarettes[3]. Smokeless tobacco products have fewer known carcinogens compared to combustible cigarettes, which are far less likely to impact lung tissue.

Side by side comparison of DNA damage and inflammation in cell lines exposed to tobacco particulate matter, wet smoke conditioned medium or smokeless tobacco extract, smokeless tobacco extract induced minimal cytotoxicity and inflammation[4]. In the three cell lines tested, cell death, caspase activity (predicting future apoptosis) and H2AX positive cell (indicating DNA repair dysfunction) are all 1000-fold less in cells exposed to smokeless tobacco extract compared wet smoke conditioned medium or

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[1] R. Borland, T. R. Partos, H. H. Yong, K. M. Cummings, A. Hyland, How much unsuccessful quitting activity is going on among adult smokers? Data from the International Tobacco Control Four Country cohort survey. *Addiction* 107, 673-682 (2012).
G. M. J. 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. *Int J Epidemiol* 46, 1948-1957 (2017).
S. H. Zhu, Y. L. Zhuang, S. Wong, S. E. Cummins, G. J. Tedeschi, E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. *BMJ* 358, j3262 (2017).
[2] Canadian Centre for Occupational health and Safety Fact Sheet: Environmental Tobacco Smoke (ETS): General Information and Health Effects *Accessed January 2019* https://www.ccohs.ca/oshanswers/psychosocial/ets_health.html
[3] M. D. Blank, T. Eissenberg, Evaluating oral noncombustible potential-reduced exposure products for smokers. *Nicotine Tob Res* 12, 336-343 (2010).
[4] S. Arimilli, B. E. Damratoski, B. Bombick, M. F. Borgerding, G. L. Prasad, Evaluation of cytotoxicity of different tobacco product preparations. *Regul Toxicol Pharmacol* **64**, 350-360 (2012).

tobacco particulate matter. Furthermore, smokeless tobacco extract induced 100- to 1000-fold less inflammation in the cell lines tested compared to the other conditions.

In addition, population studies indicate no difference in bronchiogenic or lung cancer incidence rates among attributable to snuff in smokeless tobacco users compared to non-tobacco users[5] and all cause mortality rates measured by both the NHIS and NLMS surveys show no significant difference between smokeless tobacco users and never tobacco users.

Health and warning labels benefit public health

We believe that product labels clearly acknowledging the reduced risk of Copenhagen Snuff Fine Cut compared to combusted 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 health risks associated with smoking is higher in countries with more comprehensive health warnings, which affects smoking behavior change and quit attempts[6]. It has been suggested that smokers with negative emotions towards warnings are more likely to attempt to quit[7]. However, as previously mentioned, successful one year quit rates are still rather low.

Several studies have evaluated the effects of relative risk labels of smokeless tobacco products with consistent results. Proposed labels of Snus describing the decreased relative risk compared with combustible cigarettes increased the likelihood and motivation to buy and try Snus among current smokers with little effect on former or never smokers[8]. Of particular importance is the finding that if the viewer finds the warning believable, they are more likely to act accordingly. This was true for all survey participants, but had the most effect on current smokers.

Consistent with this study are findings that labels describing the reduced risk of Snus compared to combustible cigarettes better inform users of relative harm but have no effect on the perceptions of the addiction potential of Snus – study participants are aware of reduction in potential harms without compromising the knowledge of the addiction potential of nicotine[9]. When survey participants were provided a more thorough fact sheet explaining scientific knowledge of nicotine and the relative harms of smokeless tobacco versus combustible tobacco their knowledge of both nicotine replacement therapies and smokeless tobacco versus cigarettes greatly increased, as did the likelihood that future quit attempts

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[5] G. Andreotti *et al.*, Tobacco Use and Cancer Risk in the Agricultural Health Study. *Cancer Epidemiol Biomarkers Prev* **26**, 769-778 (2017).

[6] D. Hammond, G. T. Fong, A. McNeill, R. Borland, K. M. Cummings, Effectiveness of cigarette warning labels in informing smokers about the risks of smoking: findings from the International Tobacco Control (ITC) Four Country Survey. *Tob Control* 15 Suppl 3, iii19-25 (2006).

[7] Y. J. 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, 226-234 (2018).

[8] B. Rodu, N. Plurphanswat, J. R. Hughes, K. Fagerstrom, Associations of Proposed Relative-Risk Warning Labels for Snus With Perceptions and Behavioral Intentions Among Tobacco Users and Nonusers. *Nicotine Tob Res* 18, 809-816 (2016).

[9] D. Mays, M. B. Moran, D. T. Levy, R. S. Niaura, The Impact of Health Warning Labels for Swedish Snus Advertisements on Young Adults' Snus Perceptions and Behavioral Intentions. *Nicotine Tob Res* 18, 1371-1375 (2016).

would be assisted by one of these products. This is significant because assisted quit attempts have a higher rate of success.

While studies described above are largely specific to Snus it is highly likely that results can extend to other snuff products. Data from the applicant's materials clearly demonstrate that the proposed marketing claim did not alter the study participant's perceptions of absolute risk of the products, but did positively impact their knowledge of the relative risk of lung cancer *in comparison to combustible cigarettes*.

Considering there are 2.3 million dual users *and* nearly 75 percent of dual users incorrectly believe that combustible cigarettes and smokeless tobacco products are equally harmful, there is potential that over 1.5 million people will be willing to switch entirely to a product they have already accepted.

To be certain, complete abstinence is the best way to reduce the burden of disease among smokers; unfortunately, it is very difficult to do successfully. In the commissioner's statement on the future of tobacco, he called for "innovations that have the potential to make a notable public health difference." Starting the process to approve modified-risk tobacco product marketing claims to applicants who meet the strict standards set forth by the FDA is the first step to improve the health of our populace. As such, the MRTP designation sought by U.S. Smokeless Tobacco Company LLC for Copenhagen Snuff Fine Cut could yield drastic improvements in the health of smokers.

Sincerely,
Carrie Wade, PhD, MPH
Harm Reduction Policy Director, R Street Institute

Chelsea Boyd
Harm Reduction Research Associate