FDA should not permit the U.S. Smokeless Tobacco Company to market Copenhagen Snuff with modified risk claims

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U.S. Smokeless Tobacco Co. (USSTC) submitted a Modified Risk Tobacco Product Application (MRTPA)[1] to market Copenhagen Snuff with the proposed modified risk claim, "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer." USSTC claims it presented sufficient scientific evidence in its MRTPA showing that: 1) Copenhagen snuff is significantly less harmful than cigarettes; 2) The proposed claim is accurate, non-misleading, and supported by the scientific evidence; and 3) A net benefit to the health of the population as a whole is expected when marketed with the proposed claim.

However, FDA must not grant an order allowing USSTC to market Copenhagen Snuff with its proposed modified risk claim, because the MRTPA did not meet the statutory requirements specified in section 911 of the Family Smoking Prevention and Tobacco Control Act (TCA).[2]

1. USSTC did not meet the statutory requirements for a modified risk order

To be granted a MRTP order, TCA section 911(g) requires USSTC to demonstrate that the product, as it is actually used by consumers, will both:

A) Significantly reduce harm and the risk of tobacco related disease to individual tobacco users; and
B) Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

In making its decision, FDA must take into account not only the relative health risks to individuals who use the product under consideration, but also the likelihood that current users of tobacco products who would otherwise stop using those products will switch to the product under consideration, the likelihood that non-users, including youth, will start using the product,

[1] https://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm619683.htm
[2] Family Smoking Prevention and Tobacco Control Act. Public Law 111-31 (2009), Sec. 911. http://www.gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf

and the risks and benefits of the product as compared to the use of smoking cessation products. (TCA section 911(g)(4))

Additionally, to issue an MRTP order, FDA must find that USSTC demonstrated that the proposed modified risk labeling and advertising "enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation ***to all of the diseases and health-related conditions*** associated with the use of tobacco products." (Emphasis added, TCA section 911(h)(1))

As we will describe in more detail below, ***the USSTC MRTPA did not meet these statutory requirements; therefore, FDA must not issue the requested modified risk order.***

USSTC's application presents evidence that use of moist snuff smokeless tobacco is associated with a lower risk of lung cancer than smoking cigarettes. In considering this claim, it is important to note that USSTC did not demonstrate that their proposed modified risk marketing would be effective in convincing smokers to *switch completely* to smokeless, a necessary condition for determining the validity of the claim. Additionally, ***reducing the risk of a tobacco-related disease to individual tobacco users is only one prong of the two statutory requirements that USSTC must demonstrate to be granted a MRTP order. The applicant must also demonstrate an overall public health benefit to both users and non-users, including youth, and must demonstrate that their proposed labeling and marketing messages will be understood, will not mislead, and will lead to harm reduction. USSTC's MRTPA failed to do this.***

2. USST's proposed marketing claim focuses on the lung cancer risk of using moist snuff relative to smoking cigarettes. This claim is misleading because it does not address the absolute carcinogenic potential of moist snuff.

FDA should not overlook that the International Agency for Research on Cancer (IARC) confirmed a causal role for smokeless tobacco in oral, esophageal, and pancreatic cancer.[3,4] Regarding lung cancer, while smokeless tobacco may present a lower risk than combustible tobacco, there is evidence that use of smokeless tobacco is associated with meaningfully greater lung cancer risk compared to living completely tobacco free.

[3] International Agency for Research on Cancer. Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 89 (2007). Available from: https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-32/
(accessed 10 Dec 2018)

[4] International Agency for Research on Cancer. Personal Habits and Indoor Combustions: A Review of Human Carcinogens, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100E (2012). Available from: https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-17/ (accessed 10 Dec 2018)

- Moist snuff smokeless tobacco contains the known human carcinogens 4-(methylnitrosamino)-1- (3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN).[5] NNK is a causative agent in tobacco-related lung cancer.[6]

- In a meta-analysis of three studies from the United States, smokeless tobacco was associated with a 1.8 fold increase in the risk of lung cancer, which just missed the threshold for statistical significance due to the small number of studies available.[7]

- In January 2017, the FDA published a proposed product standard that would set a limit on the amount of NNN permissible in finished smokeless tobacco products. In the FDA's own assessment of the evidence supporting the product standard, the FDA stated that the standard may reduce the risk of "other cancers such as pancreatic, laryngeal, prostate, and lung cancer."[8]

The FDA should be concerned that consumers will interpret the proposed modified risk marketing of Copenhagen moist snuff to mean that smokeless tobacco conveys no risk of lung cancer or other tobacco-related systematic cancers when in truth, smokeless tobacco is a known human carcinogen and serious health risk.

3. USSTC did not demonstrate that consumers understand the proposed modified risk claim; that it would change their perceptions of risk or intentions to try, switch, or use Copenhagen moist snuff; or that marketing Copenhagen Moist Snuff with modified risk claims would improve the health of the public overall

USSTC conducted one quantitative and two qualitative and studies (Table 1) to develop the modified risk claim and evaluate consumers' reactions to it. ***These studies do not provide sufficient evidence that it is both necessary to the marketing of their product and will not impose further harms to the public's health by increasing usage of their product by non-users, including youth.***

Table 1. Studies in **"**Perception and Behavior Program for Development and Testing of a Modified Risk Claim"

Study #	Study design	Participants	Time	Stated study goals
CCI	Quantitative (online	5,871 adult smokers, dual	May – July 2017	Primary outcomes: comprehension of the claim;

[5] Richter P, Hodge K, Stanfill S, Zhang L, Watson C. Surveillance of moist snuff: total nicotine, moisture, pH, un-ionized nicotine, and tobacco-specific nitrosamines. Nicotine Tob Res. 2008 Nov;10(11):1645-52.
[6] Hecht SS, Stepanov I, Carmella SG. Exposure and Metabolic Activation Biomarkers of Carcinogenic Tobacco-Specific Nitrosamines. Acc Chem Res. 2016 Jan 19;49(1):106-14
[7] Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. Lancet Oncol. 2008;9(7):667-75.
[8] FDA. Tobacco Product Standard for N-Nitrosonornicotine Level in Finished Smokeless Tobacco Products. Federal Register. Docket No. FDA-2016-N-2527. Document 2017-01030. https://www.federalregister.gov/documents/2017/01/23/2017-01030/tobacco-product-standard-for-n-nitrosonornicotine-level-in-finished-smokeless-tobacco-products (accessed 10 Dec 2018)

	randomized experiment)	users, moist snuff tobacco users, former tobacco users and never tobacco users		intentions to try, use, dual use, and switch to Copenhagen Secondary outcomes: risk perceptions; intentions to quit smoking/tobacco use
CS-01	Qualitative (focus groups)	63 adult male smokers who did not reject moist snuff tobacco and dual users of moist snuff and cigarettes	Feb 2015	Developing the claims
CS-01.1	Qualitative (individual interviews)	22 adult male smokers who did not reject moist snuff and dual users of moist snuff and cigarettes	April 2015	Evaluating understanding of the claims and claim's impacts on risk perceptions and behavioral intentions

Source: Module 6: Summary of All Research Findings: 6.2.: Effect of Marketing on Consumer Understanding and Perceptions

The results of all these studies indicate that the modified risk claim did not change perceptions of risk or intentions to try, switch, and use Copenhagen moist snuff. In its MTRPA, USSTC states, "Collectively, the findings suggest that, for tobacco users and non-users, a single exposure to the modified risk claim ***does not have a meaningful effect*** upon behavioral intentions and perceptions of risk."[9]

Despite its own findings, of no effect for both smokers and non-smokers, the USSTC nonetheless claims different long-term effects for these two groups. For smokers, the USSTC optimistically anticipates that the emphasis on "complete switching" and prolonged exposure to marketing information containing the modified risk claim will, over time, contribute to understanding of the accurate modified risk claim, adjustment of prior beliefs, and encouragement for adult cigarette smokers to switch to the candidate product instead of cigarettes.[10]

In contrast, for non-smokers and non-users, the USSTC likewise optimistically states that there is no reason to expect an increase in initiation of the candidate product when marketed with the proposed modified risk claim, based on the lack of interest in the candidate product by the population of non-users (adults and young adults LA-24) after exposure to that claim. USSTC states is does not anticipate youth initiation rates for the candidate product to exceed rates currently observed for the ST category.[11]

[9] USSTC MRTP Application for Copenhagen Snuff Fine Cut. Non-interventional study report, p. 14, app-7-3-2-1-ccis-report_Release in Full.pdf

[10] USSTC MRTP Application for Copenhagen Snuff Fine Cut. 2.3.: Executive Summary, p. 42, 2.3-executive summary _Redacted.pdf

[11] USSTC MRTP Application for Copenhagen Snuff Fine Cut. 2.3.: Executive Summary, p. 43, 2.3-executive summary _Redacted.pdf

It is unlikely that both of those optimistic outcomes would come true. Based on the prevalent patterns of use and transitions between smoking and smokeless tobacco use,[12] smokers will likely continue to be uninterested in smokeless tobacco, and dual users will either continue dual use or transition to exclusive smoking. In addition, the USSTC's own qualitative studies found that "only a few participants stated positive changes in intention to use [moist snuff tobacco], they were typically dual users."[13]

Furthermore, USSTC argues that it is necessary to change the risk perceptions because risk perceptions are one of the drivers of behavior. However, while the high perceived risk might prevent a behavior (as reported in the qualitative study reports: high perceived risks are a barrier to using moist snuff tobacco (MST): "Barriers to situational or exclusive use of MST varied, but initial perceptions of the risk to health were fairly consistent across all audiences"[14]), low perceived risk is not necessarily an incentive to use MST ("Discussions of potential claim statement language took place in the context of health risks not being a key driver for interest in or usage of the product"[15]). ***Therefore, if the ultimate goal is to promote smokeless tobacco to smokers, reducing perceived risk is unlikely to prove sufficient.***

The data USSTC provided did not show any differences pre- or post- viewing the control and test messages, nor were there differences between the groups that saw the control versus the test message when it came to risk perceptions.[16] While USSTC argues the need for including a modified risk message on Copenhagen moist snuff, their own data demonstrate that the message does not have an impact on risk perception. The modified risk message proposed by USSTC for Copenhagen ***does not have enough evidence to show it will motivate smokers to switch to the exclusive use of their product*** nor do they demonstrate that there will be no unintended consequences on non-smokers which will increase overall tobacco consumption. ***The FDA should not allow USSTC to make this modified risk claim without a more thorough analysis of the impact on non-smokers and the potential for an increased burden of tobacco-related diseases across all groups, but especially youth and young adults.***

There is also concern that any claims of low risk will attract non-users to the product. There is ample evidence showing that youth tobacco users perceive lower tobacco-related risk

[12] Tam J, Day HR, Rostron BL, Apelberg BJ. A systematic review of transitions between cigarette and smokeless tobacco product use in the United States. BMC Public Health. 2015;15(1):258.
[13] USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6: Summary of All Research Findings: 6.2.: Effect of Marketing on Consumer Understanding and Perceptions, p. 10, 6-2-risk-perceptions_Release in Full.pdf
[14] USSTC MRTP Application for Copenhagen Snuff Fine Cut. 7.3.3-1: CS-01- Claims Qualitative Study, p. 6, app-7-3-3-1-cs-01-claims-qual-study_Redacted.pdf
[15] USSTC MRTP Application for Copenhagen Snuff Fine Cut. 7.3.3-1: CS-01- Claims Qualitative Study, p. 6, app-7-3-3-1-cs-01-claims-qual-study_Redacted.pdf
[16] USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6: Summary of All Research Findings: 6.2.: Effect of Marketing on Consumer Understanding and Perceptions, Figure 6.2-7: General Harm Associated with the Candidate Product Pre-Post for Test and Control, p. 21, 6-2-risk-perceptions_Release in Full.pdf

than non-users,[17] including with smokeless tobacco,[18] and that non-tobacco users with low perceptions of tobacco-related risk are more likely to subsequently initiate use.[19] USSTC has not presented sufficient evidence that the proposed claims will not result in lower tobacco risk perceptions subsequent onset of smokeless tobacco use among youth. Therefore, these claims should not be allowed.

4. USSTC's proposed modified risk claim is misleading, especially to youth, and may lead to dual use with combustible tobacco

Holding a perception that smokeless tobacco is associated with a lower risk of systemic disease, such as lung cancer, in comparison to smoking cigarettes is a strong predictor of smokeless tobacco use among adolescents.[20,21,22] The proposed Copenhagen marketing that emphasizes this contrast between smokeless and combustible products has a danger of expanding smokeless tobacco use among youth, particularly rural male adolescents and young adults, who are already at elevated risk of tobacco use in all forms.

In a study of male baseball athletes at rural high schools in California, cigarettes and smokeless tobacco were perceived to convey different probabilities of risk: participants generally viewed use of *both* cigarettes and smokeless tobacco as carrying a great risk of oral health problems and great risk of getting into "trouble" (facing discipline) from parents or at school, but smokeless tobacco was viewed, on average, as having less risk of systemic ailments.[23] While this perceived difference in systemic health risks between cigarettes and smokeless tobacco was observed among both tobacco users and non-users, the difference was more pronounced among current smokeless tobacco users and smokeless/combustible dual- users. Similar results were

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[17] Song, AV, Morrell, HE, Cornell, JL, Ramos, ME., Biehl, M., Kropp, RY., Halpern-Felsher, BL. Perceptions of Smoking-Related Risks and Benefits as Predictors of Adolescent Smoking Initiation. American Journal of Public Health. 2009 Mar; 99(3):487-92. PMID: 19106420.

[18] Halpern-Felsher, BL, Biehl, M, Kropp, RY, & Rubinstein, ML. Perceived risks and benefits of smoking: Differences between adolescents with different smoking experiences and intentions. Preventive Medicine. 2004 Sep; 39(3): 559-567. PMID: 15313096.

Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, BL. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. Journal of Adolescent Health. 2016 May, 58(5):5558-66. PMID: 27107909.

[19] Song, AV, Morrell, HE, Cornell, JL, Ramos, ME., Biehl, M., Kropp, RY., Halpern-Felsher, BL. Perceptions of Smoking-Related Risks and Benefits as Predictors of Adolescent Smoking Initiation. American Journal of Public Health. 2009 Mar; 99(3):487-92. PMID: 19106420.

[20] Halpern-Felsher, BL, Biehl, M, Kropp, RY, & Rubinstein, ML. Perceived risks and benefits of smoking: Differences between adolescents with different smoking experiences and intentions. Preventive Medicine. 2004 Sep; 39(3): 559-567. PMID: 15313096.

[21] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, BL. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. Journal of Adolescent Health. 2016 May, 58(5):5558-66. PMID: 27107909

[22] Chaffee BW, Couch ET, Urata J, Gansky SA, Essex G, Cheng J. Predictors of Smokeless Tobacco Susceptibility, Initiation, and Progression Over Time Among Adolescents in a Rural Cohort. Substance Use and Misuse. 2019 (In Press).

[23] Chaffee BW, Cheng J. Cigarette and Smokeless Tobacco Perception Differences of Rural Male Youth. Tob Regul Sci. 2018 Jul;4(4):73-90.

found for a group of urban and suburban California youth.[24] In other words, ***perceiving greater harm differences was associated with smokeless tobacco use, both alone and in combination with combustible tobacco.***

Examining these data specifically for the perceived risk of lung cancer, the perceived difference in risk was greatest for users of smokeless tobacco, including dual/poly users of smokeless tobacco with other products[25] (Figure 1). Additionally, among rural high school male baseball players who had not used smokeless tobacco in the past 30-days, susceptibility to smokeless tobacco use was associated with perceiving a greater difference in lung cancer risk between cigarettes and smokeless tobacco (Table 2). ***Perceiving a greater difference in risk between cigarettes and smokeless tobacco was also positively associated with susceptibility to use of cigars, e-cigarettes, and hookah*** (Table 2).

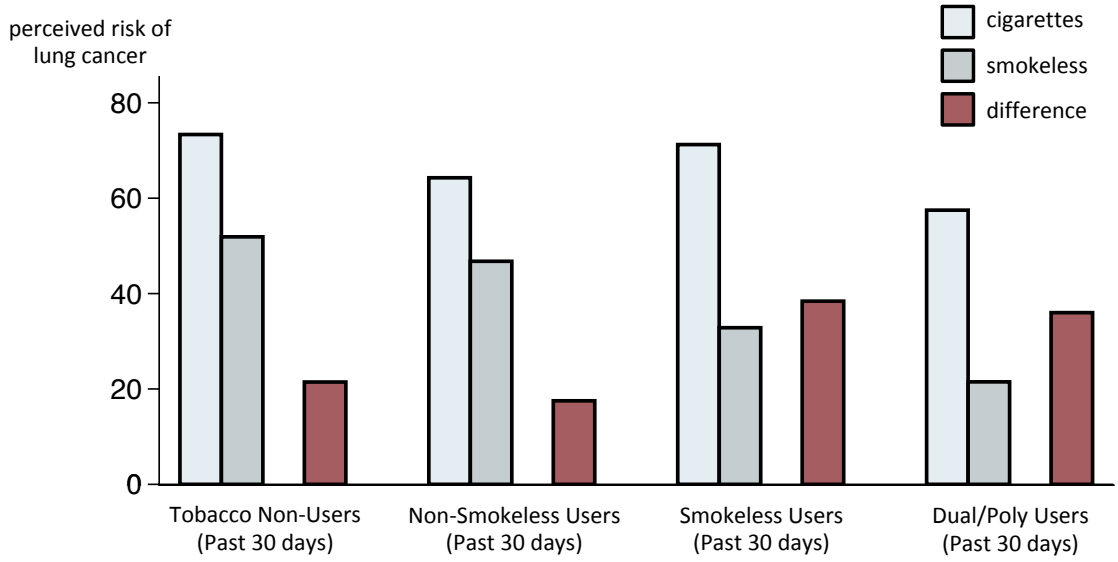

Figure 1. Perceived lung cancer risk of cigarettes and smokeless tobacco, rural male adolescents Perceived risk estimated by asking participants to imagine the chance that they were to develop lung cancer if the used cigarettes and if they used smokeless tobacco. Those participants who used smokeless tobacco, whether alone or in combination with other tobacco products, perceived a greater difference between cigarettes and smokeless.

Table 2. Differences in perceived lung cancer risk of cigarettes and smokeless tobacco according to susceptibility to use of various tobacco products, rural male adolescents

Product	Susceptibility	Cigarette Risk	Smokeless Risk	Difference	p-value (difference-in-difference)
Smokeless	susceptible	70	45	25	***0.018***

[24] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, BL. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. Journal of Adolescent Health. 2016 May, 58(5):5558-66. PMID: 27107909

[25] Chaffee BW, Cheng J. Cigarette and Smokeless Tobacco Perception Differences of Rural Male Youth. Tob Regul Sci. 2018 Jul;4(4):73-90; augmented with unpublished data

	not susceptible	73	56	17	
Cigarettes	susceptible	67	45	22	0.51
	not susceptible	73	48	24	
E-cigarettes	susceptible	70	42	28	***0.009***
	not susceptible	72	53	20	
Cigars	susceptible	69	41	28	0.05
	not susceptible	74	52	22	
Hookah	susceptible	71	40	31	***0.002***
	not susceptible	73	53	21	

Participants were considered "susceptible" to product use if answering anything other than "definitely not" to the question, if one of your best friends offered you [product], would you use it. The susceptibility question was asked separately for each tobacco product among past 30-day non-users of that product.

The prevalence of smokeless tobacco use among male US high school students is now similar to cigarettes (2017 NYTS: cigarettes 8%, smokeless tobacco 8%; 2017 YRBS: cigarettes 10%, smokeless tobacco 9%).[26] Unlike youth cigarette smoking, which has been declining steadily for the last 20 years, youth use of smokeless tobacco has largely held steady. This is a persistent problem that has been resistant to the tobacco control policies and social changes that have reduced youth cigarette smoking. USSTC attempts to paint the stagnant progress on reducing youth smokeless tobacco use in a positive light, arguing, illogically, that the persistence of youth smokeless tobacco use over this time period is not related to youth's diverging harm perceptions of smokeless tobacco relative to cigarettes.[27] ***The opposite argument is more plausible: as adolescents have grown to perceive smokeless tobacco as a more palatable alternative to cigarettes in terms of health risks, smokeless tobacco use has grown more resistant to the public health gains achieved in reducing youth smoking. USSTCs proposed reduced harm marketing campaign stands to exacerbate this problem.***

5. USSTC's proposed marketing may lead to youth appeal and uptake of smokeless and combustible tobacco products

[26] Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Queen B, Lowry R, Chyen D, Whittle L, Thornton J, Lim C, Bradford D, Yamakawa Y, Leon M, Brener N, Ethier KA. Youth Risk Behavior Surveillance - United States, 2017. MMWR Surveill Summ. 2018 Jun 15;67(8):1-114.
Wang TW, Gentzke A, Sharapova S, Cullen KA, Ambrose BK, Jamal A. Tobacco Product Use Among Middle and High School Students - United States, 2011-2017. MMWR Morb Mortal Wkly Rep. 2018 Jun 8;67(22):629-633.

[27] USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6: Summary of All Research Findings: 6.4.: Effect on Tobacco Use Initiation Among Nonusers. 6-4-effect-tobacco-use-init-nonusers_Release in Full.pdf

USSTC misleadingly claims that the evidence that youth or other non-smokers who use moist snuff or other smokeless tobacco progress to cigarette smoking is "mixed" and that the "best way" to address this risk is by allowing USSTC to conduct their own "postmarket surveillance."[28] The application did not describe what remedial action would be possible, let alone that USSTC would be motivated to take, if such "surveillance" did indeed indicate that the proposed marketing of Copenhagen moist snuff leads to expanded smokeless tobacco use among youth and/or increased cigarette smoking among individuals who were enticed to begin smokeless tobacco use. The application's failure to demonstrate adequate evidence that its proposed marketing will not lead to expanded youth tobacco use should not be solved by granting USSTC permission to guard the henhouse in the form of post market surveillance.

The real question to be addressed is whether Copenhagen Snuff, with lower perceived risks, encourages never-smokers -- including adolescents and young adults -- who would otherwise not use any tobacco products to be more likely to try smokeless tobacco product.

Exposure to modified risk claims in smokeless tobacco marketing may lead to an increase in exposure to harmful and potentially harmful chemicals among never- and former-smokers, including adolescent never-smokers who might initiate nicotine use with smokeless tobacco. This is something of great concern that USSTC didn't take into account.

Importantly, USSTC's proposed claims introduce language ("switching completely" and "reduces risk") that is unlikely to be familiar to adolescents and youth. It is essential that the USSTC demonstrate that such claims will be understood by youth and that consumers' (or potential consumers') interpretations of these claims are aligned with the actual risks of the smokeless tobacco. The language used in these claims must be tested thoroughly among the entire population for salience, credibility, readability, and accuracy of consumers' interpretations. In particular, there is reason to believe that potential consumers will misunderstand the concept of "switching completely." For example, many individuals who engage in smoking do not consider themselves to be smokers,[29] including large numbers of young adult smokers and >12% of all adult smokers in California.[30] Smoking cigarettes but not identifying as a smoker is common among non-daily smokers who were formerly daily smokers,[31] opening the likelihood that smokeless tobacco users may consider themselves to have "switched completely" even if they continue to smoke combustible cigarettes.

Further, the USSTC application does not provide any reliable information on whether adolescents would be more interested in using smokeless tobacco, especially after viewing the

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[28] USSTC MRTP Application for Copenhagen Snuff Fine Cut. 2.3.: Executive Summary. 2.3-executive summary _Redacted.pdf

[29] Leas EC, Zablocki RW, Edland SD, Al-Delaimy WK. Smokers who report smoking but do not consider themselves smokers: a phenomenon in need of further attention. Tob Control 2015;24(4):400-3 ; Guillory J, Lisha N, Lee YO, Ling PM. Phantom smoking among young adult bar patrons. Tob Control 2017;26(2):153-7 (PMC PMC5067225)

[30] Leas EC, Zablocki RW, Edland SD, Al-Delaimy WK. Smokers who report smoking but do not consider themselves smokers: a phenomenon in need of further attention. Tob Control 2015;24(4):400-3

[31] Leas EC, Zablocki RW, Edland SD, Al-Delaimy WK. Smokers who report smoking but do not consider themselves smokers: a phenomenon in need of further attention. Tob Control 2015;24(4):400-3

claims, if adolescents would initiate nicotine use with smokeless tobacco, if adolescents would switch from another tobacco product to smokeless tobacco, or if adolescents would use moist snuff along with other tobacco products.

One way to obtain information on adolescents' interests and behavior is to conduct studies with adolescents. However, no tobacco company should be permitted to conduct research on youth below the legal age for tobacco use (21, to be conservative) because they could use such information to design marketing campaigns to attract youth to their products. A different way to get at adolescents' interest and behavior is relying on research on other, similar products, such as electronic cigarettes, conducted with no direct or indirect involvement of tobacco companies or their agents.[32]

Because the application did not consider the impact of smokeless tobacco on adolescent use, it did not demonstrate that the product,* as actually used by consumers*, will benefit the health of the population as a whole, including current non-users; in particular, it did not provide any scientific evidence regarding the effect that this product and its marketing would have on increasing the likelihood that adolescents who are currently not tobacco users will start using smokeless.

Despite section 911(g)'s requirement, this application failed to provide adequate scientific evidence demonstrating that their moist snuff products would "benefit the health of the population as a whole," in particular non-users (including adolescents) as well as current users of other tobacco products.

USSTC further misleadingly claims that smokeless tobacco use "has been shown not to predict cigarette smoking after adjusting for factors that typically influence smoking" and that smokeless tobacco use "has been associated with lower likelihood of smoking progression."[33] However, the application is dismissive of multiple longitudinal studies from the United States that demonstrate exactly the opposite: youth who use smokeless tobacco products are at increased risk of smoking combustible cigarettes in the near future, including after adjustment for multiple smoking-related risk factors.

- In a longitudinal school-based study of male 7th and 9th grade students, youth who had never smoked a cigarette but had used smokeless tobacco in the prior month at baseline had 2.6 times greater odds of cigarette smoking at least weekly 2 years later, after adjusting for multiple known risk factors for smoking initiation, such as age, family and peer smoking, alcohol use, grades in school, and other behavioral risks.[34]

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[32] Institute of Medicine. 2012. Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, DC: The National Academies Press. https://doi.org/10.17226/13294.

[33] USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6: Summary of All Research Findings: 6.4.: Effect on Tobacco Use Initiation Among Nonusers: Section 6.4.3: The Likelihood that Nonusers Who Adopt the Tobacco Product Will Switch to Other Tobacco Products That Present Higher Levels of Individual Health Risk. 6-4-effect-tobacco-use-init-nonusers_Release in Full.pdf

[34] Severson HH, Forrester KK, Biglan A. Use of smokeless tobacco is a risk factor for cigarette smoking. Nicotine Tob Res. 2007 Dec;9(12):1331-7.

- In analysis of the PATH data, among Wave 1 never-smoking youth, ever-use of smokeless tobacco was associated with 1.7 times greater odds of ever smoking cigarettes and 2.1 times greater odds of past 30-day cigarette smoking after 1 year of follow-up, after adjusting for use of any other form of tobacco, age, sex, race/ethnicity, and several other smoking risk factors.[35] In a different approach to the data, the authors also reported that use of smokeless tobacco only (no other tobacco products) was associated with 1.9 times greater odds of cigarette smoking one year later, after adjusting for known risk factors, albeit not statistically significant due to the smaller sample size.[36] In contrast, the USSTC application, misleadingly claimed that this study "suggest[s] no specific relationship linking ST use with smoking onset."[37]

- In a national study of nearly 4000 US males age 11-19, regular use of smokeless tobacco among non-smokers at baseline was associated with 3.5 times greater odds of current regular cigarette smoking 4 years later, after adjusting for age and race/ethnicity.[38]

Despite citing all of these publications in its application, as well as others showing a positive association between smokeless tobacco use and future smoking in youth and young adults,[39] ***USSTC claimed the opposite of what these papers found.***

In addition, USSTC argues that: "A harm reduction strategy that informs adult smokers about reduced risk products, subject to FDA oversight, will *complement*, not *compete*, with proven prevention and cessation strategies."[40] However, it is likely that these modified risk messages will be seen by youth. As such, they *will directly compete*, not *complement* the FDA's proven prevention strategies, specifically, the Real Cost campaign, which has been

[35] Watkins SL, Glantz SA, Chaffee BW. Association of Noncigarette Tobacco Product Use with Future Cigarette Smoking Among Youth in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2015. JAMA Pediatr. 2018 Feb 1;172(2):181-187.
[36] Watkins SL, Glantz SA, Chaffee BW. Association of Noncigarette Tobacco Product Use with Future Cigarette Smoking Among Youth in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2015. JAMA Pediatr. 2018 Feb 1;172(2):181-187.
[37] USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6: Summary of All Research Findings: 6.4.: Effect on Tobacco Use Initiation Among Nonusers: Section 6.4.3.1: ST Use Has Been Shown Not to Predict Cigarette Smoking After Accounting for Other Factors That Typically Influence Smoking. 6-4-effect-tobacco-use-init-nonusers_Release in Full.pdf
[38] Tomar SL. Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. experience. Nicotine Tob Res. 2003 Aug;5(4):561-9.
[39] Haddock CK, Weg MV, DeBon M, Klesges RC, Talcott GW, Lando H, Peterson A. Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males. Prev Med. 2001 Mar;32(3):262-7.
Soneji S, Sargent JD, Tanski SE, Primack BA. Associations between initial water pipe tobacco smoking and snus use and subsequent cigarette smoking: results from a longitudinal study of US adolescents and young adults. JAMA Pediatr. 2015 Feb;169(2):129-36.
[40] USSTC MRTP Application for Copenhagen Snuff Fine Cut. 2.3.: Executive Summary, p. 6, 2.3-executive summary _Redacted.pdf

communicating to youth at-risk for smokeless tobacco use that "smokeless doesn't mean harmless."[41]

The FDA should not rely on the misleading bulleted conclusions presented in USSTC's MRTPA that run counter to the cited literature. Instead, in weighing the total public health impact of the proposed Copenhagen moist snuff marketing, ***the FDA should account for the fact that to any extent the marketing increases the uptake of smokeless tobacco among non-smokers, especially youth, those new smokeless tobacco users will be at risk of future combustible smoking, as well.***

6. USSTC's evidence that adult smokers "misperceive" the harm of smokeless tobacco products relative to cigarettes is insufficient to demonstrate that marketing Copenhagen Snuff with modified risk claims would improve the health of the public

USSTC emphasizes that adult smokers "misperceive" the harm of smokeless tobacco relative to cigarettes, arguing that many US adults, including cigarette smokers, believe that using smokeless tobacco to be equally harmful to smoking cigarettes. However, ***evidence of such a misperception is insufficient to demonstrate that marketing Copenhagen moist snuff with a reduced harm claim will improve the health of the public overall.*** Quite the contrary, the application:

- Fails to demonstrate that such a perception is an impediment to smokers choosing to use smokeless tobacco as a substitute for cigarette smoking
- Fails to demonstrate that changing smokeless tobacco harm perceptions will encourage current smokers to switch completely from smoking to using smokeless tobacco
- Provides no evidence that the proposed marketing messages would either change current adult smokers' perceptions of smokeless tobacco harms or increase their likelihood of switching completely to moist snuff instead of smoking

Even if there is a "misperception" among US adults about smokeless tobacco harms relative to cigarettes, USSTC's MRTPA does not provide adequate evidence that the proposed marketing will meaningfully improve the health of current adult cigarette smokers. Simultaneously, the application greatly downplays the risk that such marketing will increase the use of moist snuff among current non-smokers, including youth, and that it will encourage current smokers who otherwise would have quit use of all tobacco products instead to use moist snuff, alone or in dual-use with cigarettes.

7. USSTC's dynamic population model does not support issuing a MRTP order

[41] FDA's The Real Cost Campaign. Know the real cost of tobacco. https://therealcost.betobaccofree.hhs.gov/dip

USSTC relies on a model developed for Altria Client Services LLC (ALCS) to estimate the population impact of their MRTPA. (USSTC is an Altria subsidiary.) While the FDA indicates that "applicants may opt to use currently available models in the scientific literature to forecast the harm to public health from tobacco use,"[42] the ALCS Cohort Model does not meet this criterion.

The ALCS Cohort Model has not been published in the peer-reviewed literature; rather it is documented only in a conference poster.[43] The model is used to assess all-cause mortality for a base case using male cigarette and moist smokeless tobacco (MST) product behaviors and a modified case scenario which reflects predicted changes in transition rates for cigarettes and MST that would occur with the proposed MRTP claims. The model is limited to a US native-born male population and considers only mortality outcomes.[44] Is uses a single cohort as well as a time-staggered multi-cohort approach. Assuming that the product will retain its current market share after 60 years -- a very questionable assumption given the highly dynamic nature of the tobacco products market -- the multi-cohort model projects an expected net benefit of 7,500 additional survivors from a starting cohort of 1 million native-born males after 60 years. The model is developed following recommendations for model development from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM).[45] A number of sensitivity analyses are conducted (transition probabilities between tobacco use categories and survival probabilities) and the model is validated using US Life Tables for 2006. ***However, the model can be no better than the assumptions it incorporates. There are problems with assumptions 9+and inputs used in the model.***

The ALCS Cohort Model includes native-born males only. It is not clear why other males are not included, but this omission will lead to a difference in net benefits. The MRTPA indicates that they will "provide justification for our population of interest (i.e. the US native-born male population) in Section 7.4.2.2.3".[46] However, no such justification is provided. It is not clear whether this restriction in population will result in an overestimate or an underestimate.

Furthermore, ***ALCS does not include females in their analyses***, justifying the exclusion by indicating that 95% of adult MST users were male according to the 2014 National Survey on Drug Use and Health.[47] While this is correct, the modified risk statement may attract more

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[42] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. Guidance for Industry. Modified Risk Tobacco Product Applications. Draft Guidance., 2012.
[43] Boone RJ, Muhammed-Kay RS PY, Wei L, et al. Combining statistical and compartmental models for use in tobacco product risk assessments. Paper presented at the Conference on Statistical Practice, San Diego, 2016.
[44] Altria Client Services LLC. USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6.5: Population Health Model Research Summary.
[45] Caro JJ, Briggs AH, Siegert U, et al. Modeling good research practices- overview: A report of the ISPOR-SMDM modeling good research practices task force - 1. Medical Decision Making 2012;32(5):667-77.
[46] Altria Client Services LLC. USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6.5: Population Health Model Research Summary. (page 5)
[47] Altria Client Services LLC. USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6.5: Population Health Model Research Summary. (page 5)

females to use the product, including those who do not currently use tobacco. ***This would result in an increase in negative health outcomes, an impact that is not considered.***

The model only considers mortality, despite the fact that tobacco use (including snus) causes considerable morbidity. This is contrary to FDA guidance that explicitly directs that estimates of the effect of an MRTP include the effect on overall tobacco-related morbidity and mortality.[48] The ALCS Cohort model does not include any measures of morbidity, including tobacco-caused disease incidence or tobacco-attributable healthcare costs. Wang et al.[49] found that smokeless tobacco use, including chew, snuff, and snus, accounted for over $3.4 billion in excess annual healthcare expenditures, including $1.8 billion for hospitalizations. $0.7 billion for emergency room visits, and $0.9 billion for doctor visits (2014 dollars). While this study was not able to separately estimate costs attributable to snus use, the findings suggest that these costs could be substantial. ***Ignoring disease morbidity resulting from snus use underestimates its impact on health and medical costs.***

The mortality models are based on data from the Kaiser Permanente Medical Care Program Cohort study and appear to reflect mortality ratios for insured individuals in 1991. These rates were then adjusted "by assigning weights that reflect mortality rates in the US population."[50] Mortality rates for cigarette smoking from the early 1990's are likely to be much higher than the comparable rates today due to changes in cigarettes, changes in other tobacco use patterns, and changes in intensity of cigarette smoking. ***Using these rates as the basis for determining excess relative risks for MST vs. cigarette smoking will lead to an overestimate of lives saved.***

Dual users of cigarettes and MST are assumed to have the same relative risk of mortality as sole cigarette smokers. The potential additive effect of using multiple products is not considered. Dual use of smokeless tobacco (ST) products (including SNUS) and other products is common. According to an analysis of the 2012-14 National Adult Tobacco Survey,[51] 3.6% of U.S. adults aged 18+ were current ST users (See Table 1 of the cited paper). Among these current ST users, 52.4% of them concurrently used one or more other tobacco products. ***By ignoring the additive risk of using both SNUS and other tobacco products, the negative impact on population health is likely underestimated.***

Other tobacco products are not included in the model to limit the number of transitions that need to be considered. It is assumed that "much of poly-tobacco use is occasional; thereby not impacting the health effects as much as regular use of cigarettes."[52] E-cigarette use is very

[48] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. Guidance for Industry. Modified Risk Tobacco Product Applications. Draft Guidance., 2012. (p. 21-22)

[49] Wang Y, Sung H, Yao T, et al. Healthcare expenditures attributable to smokeless tobacco use among U.S. adults. Nicotine Tob Res 2017 [Epub ahead of print]

[50] Altria Client Services LLC. USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6.5: Population Health Model Research Summary. (page 10)

[51] Sung HY, Wang Y, Yao T, et al. Polytobacco use and nicotine dependence among U.S. adults, 2012-2014. Under review 2018.

[52] Altria Client Services LLC. USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6.5: Population Health Model Research Summary. (page 11)

common, and because e-cigarettes are likely to have a lower mortality risk than cigarettes, the excess relative risk of MST vs. e-cigarettes may be positive or negative, and switching from e-cigarettes to MST would have a very low or possibly negative population health effect.

The model does not include the impact of snus on non-users of tobacco products, as required by the FDA.[53] This would include infections from exposure to expectorate or environmental waste. Omitting the impact of snus use on non-tobacco users will lead to an underestimation of the harm to the population of the proposed modified risk claim.

Transition rates between different tobacco use categories (e.g. never tobacco users, current cigarette and/or MST users, former cigarette and/or MST users, etc.) are critical parameters in the ALCS Cohort Model, but the rates used for the base case are obtained from published studies from 2002, 2003, and 2009.[54] In fact, the data these studies are based on are from 1993 to 2003, i.e. 15-25 years old. ***The tobacco landscape has changed considerably in recent years, and rates based on dated studies are likely to lead to incorrect estimates of the population health impact.***

The transition rates used for the modified case are based on the ALCS CCI study. However, as discussed earlier in this comment (see Section 3), the findings do not demonstrate that consumers are likely to change their perceptions of or intentions to use Copenhagen moist snuff as a result of the proposed modified risk claim. The extensive discussion provided in the MRTPA related to the impact of the modified risk claim on the population groups of interest[55] is not relevant given that the CCI study does not indicate that any changes in behavior are likely to occur.

In summary, the ALCS Cohort Model follows recommended approaches for model development but leaves out some important components and uses questionable input values and assumptions. The resulting estimates of the impact of the proposed modified risk claim for Copenhagen snuff are likely to overestimate the benefit and underestimate the costs, and do not justify the granting of the MRTP proposed.

USSTC's modified risk claim is premised on the assumption that a meaningful number of current smokers would switch completely from cigarettes to Copenhagen Moist Snuff; however, the MRTPA did not demonstrate that current smokers will switch to smokeless tobacco.

USSTC's interpretation of their "Claim Comprehension and Intentions" study (CCI) findings is an attempt to "play it both ways."

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[53] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. Guidance for Industry. Modified Risk Tobacco Product Applications. Draft Guidance., 2012.
[54] Altria Client Services LLC. USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 7.4.2: Population Model. (page 62)
[55] Altria Client Services LLC. USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6.5: Population Health Model Research Summary. (pages 65-73)

- When the study found few statistically significant changes in harm perceptions among study participants shown the proposed reduced risk statement, USSTC claimed that their proposed marketing will not increase interest in smokeless tobacco use among tobacco non-users.
    - Notably, the *only* subset of the CCI study population for which the test group reported a statistically significant decrease in the perception that smokeless tobacco "negatively impacts health" was young adult tobacco non-users.[56]

- However, in response to finding that the proposed marketing caused few or no statistically significant changes in perceptions among adult cigarette smokers (the population that would *need* to be convinced to switch completely from cigarettes to smokeless tobacco for there to be any chance of a population health benefit), USSTC claimed that the "single exposure" marketing featured in the CCI study was not representative of the "repeated exposures [that] would likely be needed in order for the information to permanently alter beliefs."[57]

Conclusion

The FDA should not approve the proposed marketing order because USSTC has shown no evidence that the proposed marketing will encourage current smokers to switch completely to smokeless tobacco. Further, there is not sufficient evidence to assure that the proposed marketing will not have a harmful effect on youth by encouraging initiation of moist snuff use, alone or in dual use with combustible tobacco. USSTC implies, without evidence, that the repeated exposure of an extended marketing campaign will lead to the desired harm reduction behavior among adult cigarette smokers but will not lead to expanded smokeless tobacco use among tobacco non-users and youth. The studies USSTC conducted do not test this assertion. If this unproven marketing campaign is approved and the result is greater smokeless tobacco use but without harm reduction, the only remedy USSTC suggest is "post market surveillance" (void of any details on how such surveillance would be conducted). As seen during the current "epidemic" of youth e-cigarette use, potential *ex post facto* solutions are severely limited. ***The FDA should not put faith in USSTC's ability or willingness to put the genie back in the bottle once widespread, untested marketing campaigns have been rolled out across the country and are shown to boost smokeless tobacco sales without appreciable reductions in cigarette smoking.***

[56] USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6: Summary of All Research Findings: 6.2.: Effect of Marketing on Consumer Understanding and Perceptions, Table 6.2-4, p. 22, 6-2-risk-perceptions_Release in Full.pdf

[57] USSTC MRTP Application for Copenhagen Snuff Fine Cut. Module 6: Summary of All Research Findings: 6.2.: Effect of Marketing on Consumer Understanding and Perceptions: 6.2.4.1.: Claims Language Development & Assessment, 6-2-risk-perceptions_Release in Full.pdf