

Docket Number: FDA-2017-N-4678-0001

Clinical Trials and Observational Epidemiology Indicate that Allowing Snus to be Marketed with Modified Risk Claims is Unlikely to Confer Population Benefit and May Cause Harm by Depressing Smoking Cessation

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August 23, 2018

Section 911(g) of the Family Smoking Prevention and Tobacco Control Act¹ and FDA's Guidance for Industry on Modified Risk Tobacco Product (MRTP) Applications² (Guidance) spell out ***two rigorous requirements*** that MRTP applicants must meet before FDA will issue an order permitting it to be marketed with reduced risk claims. In particular, to market Camel Snus with its proposed MRTP claims, RJR must demonstrate using substantial and objective scientific evidence that the new product, ***as it is actually used by consumers***, will:

- (1) Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; ***and***
- (2) 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.¹

The statutory mandate is clear: FDA can issue a MRTP order "***only if***"¹ applicants submit sufficient scientific evidence demonstrating both prongs of the requirement. RJR's MRTP application provides several lines of evidence to argue that using Camel Snus exclusively would be less harmful than smoking cigarettes for *individual* tobacco users. ***Even if RJR is correct, FDA must not issue a MRTP order for Camel Snus because RJR did not and cannot demonstrate, as required by TCA section 911(g)(1)(B), that Camel Snus, as it is actually used by consumers, will benefit the health of the population as a whole, taking into account both users and non-users, including youth. RJR's application fails because it did not demonstrate benefit to population health, whether or not it demonstrated reduced harm to individuals.***

To address the effect that the product and its marketing may have on current users, the Guidance says MRTP applicants should submit scientific studies that inform FDA's evaluation of the products impact on tobacco use behavior, including:

- The likelihood that current tobacco product users will start using the product;
- The likelihood that tobacco users who adopt the product will switch to or switch back to other tobacco products that present higher levels of individual health risk;

¹ Family Smoking Prevention and Tobacco Control Act, 21 U.S.C. §387k, Pub. L. 111-31, 123 Stat. 1776 (2009).

² Food and Drug Administration, Modified Risk Tobacco Product Applications, Draft Guidance (March 2012). Available at <https://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf>

- The likelihood that consumers will use the product in conjunction with other tobacco products [i.e., “dual use” or “poly use”];
- The likelihood that users who may have otherwise quit using tobacco products will instead use the product; and
- The likelihood that consumers will use the product as intended or designed.²

To address the effect that the product and its marketing may have on tobacco use initiation among non-users (including never users, former users, and youth), the Guidance says MRTP applicants should submit scientific studies designed to provide evidence regarding the likelihood of population benefit or harm from the proposed product, including:

- The likelihood that consumers who have never used tobacco products, *particularly youth and young adults* will initiate use of the tobacco product;
- The likelihood that non-users who adopt the tobacco product will switch to other tobacco products that present higher levels of individual health risk; and
- The likelihood that former users of tobacco products will re-initiate use with the tobacco product.²

RJR’s MRTP application does not convincingly demonstrate that marketing Camel Snus as a modified risk tobacco product will result in a net benefit to public health. **The most probable pattern of snus uptake, as actually used by consumers, is unlikely to result in meaningful population benefit and could result in net population harm** compared to the status quo, because:

- Snus products are already available to US smokers who wish to use them for harm reduction.
- Current combustible tobacco users are unlikely to switch completely to snus, but instead are more likely to follow a pattern of dual-use.
- Using snus in combination with cigarettes is likely to depress quitting smoking.
- Modified risk marketing claims may increase snus uptake among tobacco non-users, including youth.
- Youth who initiate smokeless tobacco use are at increased risk of subsequently smoking cigarettes.

The potential population health benefit of marketing Camel Snus under this MRTP applies to a very limited segment of the U.S. population.

Potential benefits apply only to individuals who:

- Are currently smoking cigarettes but are willing to quit cigarettes,
- *And* would not otherwise have quit smoking through less-toxic, FDA-approved nicotine replacement or prescription medications, behavioral counseling, cold turkey, or other means,
- *And* have not already switched to available snus products,
- *But* would switch to snus *only if* it were marketed with reduced risk claims,

- *And* would switch completely to snus rather than becoming dual-users.

Potential benefits to this narrow subset of the population must be weighed against plausible population harms, including:

- Combustible tobacco smokers who would forgo quitting in favor of snus
- Combustible tobacco smokers who would forgo quitting in favor of dual-use of cigarettes with snus
- Tobacco non-users, including youth, who would begin nicotine use with snus
- Tobacco non-users, including youth, who would begin using other tobacco products, including cigarettes and non-snus moist snuff, as a result of cross-over appeal of snus marketing or initial experimentation with snus

The existing epidemiologic evidence indicates that, as actually used by consumers, snus is unlikely to confer a net benefit to population health. Therefore, FDA should not issue an order allowing RJR to market Camel Snus with MRTP claims.

Snus Randomized Controlled Trials Assessing Smoking Cessation Among Cigarette Smokers, Including RJR's Own Studies, Do Not Support the Claim that Snus Assists Cessation. Providing Reduced Harm Information Did Not Improve Outcomes.

In a well-powered, randomized controlled trial, conducted independently of the tobacco industry, Carpenter and colleagues found that free Camel Snus distributed to cigarette smokers resulted in depressed quit attempts and no improvement in smoking abstinence.³

In this study:

- Cigarette smokers assigned to the snus intervention *were informed* how and why snus might be considered less harmful than cigarettes
- Camel Snus was provided to the intervention group for free for up to 6 weeks; the control group did not receive any form of product
- 82% of smokers in the intervention group tried snus, but only 16% were using "regularly" (6-7 days of the past week) at the end of the 6-weeks; and only 4% were using snus at all after 12 months
- Smokers assigned to the snus intervention were statistically significantly less likely to make any cigarette quit attempt (26% snus group vs. 31% control)
- There were no statistically significant differences between groups in cigarette abstinence at any time point measured
- There was no snus benefit in reducing the number of cigarettes smoked per day: the percentage of smokers cutting their cigarette consumption by 50% was essentially the same in each group (22% snus group vs. 23% control)

³ Carpenter MJ, Wahlquist AE, Burris JL, Gray KM, Garrett-Mayer E, Cummings KM, Alberg AJ. Snus undermines quit attempts but not abstinence: a randomised clinical trial among US smokers. *Tob Control*. 2017 Mar;26(2):202-209.

In an analysis of data from that same trial, Meier and colleagues reported that smokers perceived snus as a "poor substitute" for smoking, including those smokers who used snus persistently.⁴ This study directly contradicts RJR's claim that U.S. smokers would find snus appealing and would switch completely from smoking or stop smoking as a result of being informed that snus was less harmful than cigarettes.

In its MRTP application RJR cites the Carpenter et al. study to conclude: "This study illustrates that the perception of a potential health benefit of Camel Snus compared to continued smoking may be an important determinant of snus use and potential substitution for cigarettes" (Executive Summary p. 84). This is not an accurate characterization of the results in the Carpenter et al study. Carpenter, et al. did not report information on perceptions of potential risks or benefits of snus. The trial yielded negative findings even when participants were informed how and why snus might be considered less harmful than cigarettes.

Meier, et al. did report risk perceptions among the study treatment group (participants who received free snus), but found no significant differences in risk perceptions of snus among those who only experimented with snus vs. those who became "persistent" users. While not statistically different, the mean perceived risk of snus was actually higher among persistent users. This contradicts the RJR claim that holding a lower risk perception of snus is an important determinant of snus use.

In another randomized controlled trial conducted independently of the tobacco industry, Hatsukami and colleagues assigned daily cigarette smokers interested in quitting either to receive free Camel Snus or free nicotine gum.⁵ In this study:

- Use of the provided products was high (at 12 weeks: 80% for snus; 87% for nicotine gum).
- In the snus group, dual use of snus and cigarettes at 12-weeks (53%) was much higher than use of snus alone (27%) or quitting tobacco completely (9%).
- Cigarette quitting was somewhat depressed, but not statistically significantly different, for snus compared to nicotine gum for all cessation outcomes at all time points.
- Snus was associated with less satisfaction and less psychological reward compared to nicotine gum.
- The snus group, on average, was exposed to higher levels of carcinogenic tobacco specific nitrosamines than was the nicotine gum group.

Hatsukami et al concluded that, "***These findings suggest that snus performs no better than nicotine gum as a cigarette substitute, has less appeal, is more toxic and is associated with higher rates of prolonged use.***"⁶

⁴ Meier E, Burris JL, Wahlquist A, Garrett-Mayer E, Gray KM, Alberg AJ, Cummings KM, Carpenter MJ. Perceptions of Snus Among US Adult Smokers Given Free Product. *Nicotine Tob Res.* 2017 Dec 13;20(1):22-29.

⁵ Hatsukami DK, Severson H, Anderson A, Vogel RI, Jensen J, Broadbent B, Murphy SE, Carmella S, Hecht SS. Randomised clinical trial of snus versus medicinal nicotine among smokers interested in product switching. *Tob Control.* 2016 May;25(3):267-74.

In contrast to the study's actual conclusion, RJR summarized this trial's findings in its MRTTP application, stating that this trial (and two smaller pilot studies) of Camel Snus "show comparable relative potential for promoting cigarette abstinence" (Executive Summary page 165). *The FDA should rely on the conclusions in the study itself rather than RJR's characterization of the results.*

RJR's mischaracterization of the Hatsukami, et al. and Carpenter et al. studies raises concerns about the accuracy with which RJR presents the overall research base.

A third randomized controlled trial was funded by Reynolds America Inc. and co-authored by RAI researchers. In the trial, Nelson and colleagues reported that daily cigarette smokers were assigned to one of three groups and provided either: 1) nicotine lozenges, 2) Camel Snus, or 3) Camel Snus with information explaining that smokeless tobacco is less harmful than smoking cigarettes.⁷ In this study:

- Follow-up was poor, with about 2/3rds of participants not completing the study, an unusually high level of loss to follow-up (in comparison, the Carpenter, et al. trial completed 87% of all follow-up phone calls and retained 80% of the sample at the 12-month assessment⁸).
- Most of those lost to follow-up in the RAI trial were *dropped from the study by the investigators* ("not invited to the return visit") after being classified as "treatment failures," a term that was not defined in the manuscript. *The unexplained rationale for excluding much of the study population from analysis casts doubt on the validity of the findings.* Although not explicitly stated, the exclusions likely limited follow-up to individuals who were using the assigned study products, a selection bias that greatly diminishes generalizability. Notably, the fact that many participants were not invited back is buried in Supplemental material. The main manuscript only states "failure to present for assessment" as the main reason for attrition, without mentioning the investigators' role in depressing follow-up.
- Regardless of these problems, quitting smoking was statistically significantly *lower* in both snus groups than in the nicotine lozenge group, as measured by point prevalence at 12 weeks. At all other time points, abstinence was low in all groups and not statistically significantly different.
- There were no statistically significant differences in the number of cigarettes smoked per day across the three groups.
- While the mean number of cigarettes smoked per day meaningfully decreased over time in all groups, including the nicotine lozenge control, this finding applies only to

⁶ Hatsukami DK, Severson H, Anderson A, Vogel RI, Jensen J, Broadbent B, Murphy SE, Carmella S, Hecht SS. Randomised clinical trial of snus versus medicinal nicotine among smokers interested in product switching. *Tob Control*. 2016 May;25(3):267-74.

⁷ Nelson PR, Chen P, Battista DR, Pillitteri JL, Shiffman S. Randomized Trial to Compare Smoking Cessation Rates of Snus, with and without Smokeless Tobacco Health-Related Information, and a Nicotine Lozenge. *Nicotine Tob Res*. 2018 Jan 24.

⁸ Carpenter MJ, Wahlquist AE, Burris JL, Gray KM, Garrett-Mayer E, Cummings KM, Alberg AJ. Snus undermines quit attempts but not abstinence: a randomised clinical trial among US smokers. *Tob Control*. 2017 Mar;26(2):202-209.

individuals whom RAI investigators invited back for follow-up visits. It is unknown what the results would be in a generalizable cohort, in which "treatment failures" were not dropped from the study.

Thus, RAI's study does not support RJR's contention in its MRTP application that snus will assist smokers in quitting or in reducing the number of cigarettes smoked per day, even if smokers are informed that snus is less dangerous than cigarettes.

The published trial from Nelson and colleagues just discussed shares many similarities with study CSD1010 described in RJR's MRTP application, which may be the same trial. However, because Module 6 of the application has not been posted online as of August 20, 2018, it is not possible for the public to examine all of the the specifics of study CSD1010.

As stated in the application Executive Summary regarding CSD1010 (page 165):

- "Continuous cessation rates at 6 and 12 months were low (1.4% for Camel Snus, 0.9% for lozenges) and no statistical differences were observed between study products at either time point for any of the cessation criteria defined in the study protocol."
- In RJR's own exploratory analyses, which defined abstinence as not smoking after 9 months of follow-up, abstinence in the two snus groups (5.5% in both groups) was statistically significantly depressed compared to the nicotine lozenge group (10.8%), in which quitting was about twice as common.
- ***Providing reduced harm information resulted in no difference in reported outcomes***

Thus, a careful reading of RAI's results shows that the findings do not support RJR's claim in the MRTP application that the modified risk marketing proposed in this application will improve population health beyond any possible benefit already achievable from snus under current marketing. Indeed, RJR's own data do not support the proposition that snus is likely to increase quitting cigarettes at all.

Snus Observational Epidemiology Among Cigarette Smokers

Dual use of cigarettes and snus together is much more common than switching completely from cigarettes to snus. While the proposed Camel Snus advertisements stress that smokers should *switch completely* to snus to lower their risk, switching completely is a rare behavior, including in RJR's own studies. It is unlikely that most smokers will achieve this behavior. ***All three of RJR's proposed advertising executions include the condition that smokers must "switch completely" from cigarettes to Camel Snus to achieve the claimed reductions in harm and tobacco-related diseases, but RJR has not demonstrated that this condition is generally met as the product is actually used by consumers. Thus, based on RJR's own data, FDA should deny RJR's MRTP application for Camel Snus.***

Biener and colleagues reported prevalent patterns of snus use in 2011-2012 in two US metropolitan areas (Dallas and Indianapolis) where snus marketing and availability were well

established.⁹ The authors used mail and telephone surveys of more than 5000 adults and reported that:

- Ever having tried snus was not common (6%), nor was having ever used snus >20 times (4.6%) or current use (<1%)
- Current snus use among current and former cigarette smokers was "virtually absent" (<1%), suggesting that long-term snus uptake and complete switching to snus was rare for cigarette smokers
- Snus trial and ever use (>20 times) were much more common among users of conventional (non-snus) smokeless tobacco than among cigarette smokers; after adjusting for use of smokeless tobacco, cigarette smoking was not statistically significantly associated with ever using snus
- Among male cigarette smokers, snus use was associated with smoking slightly fewer cigarettes per day (ever snus use: 16.1; never or trial use: 17.0), but this association was not statistically significant in adjusted models
- Neither male nor female smokers cited quitting or cutting down smoking as their top motivation for trying snus. Male smokers who tried snus cited curiosity (41%), free sample or coupon (30%), trying to quit or cut down cigarettes (26%), and using where smoking is prohibited (20%). Female smokers who tried snus were more likely to report wanting to use in smoke-free areas (50%) than quit or cut down smoking (3%)
- Most respondents (75%) endorsed preferring another form of tobacco as their reason for not continuing to use snus after trying it, suggested limited appeal of snus to smokers
- Of the few smokers who were also current snus users, nearly all (98%) said they were using snus to reduce their cigarette smoking, but most (84%) expected to be smoking in 12 months

This observational study, which, to our knowledge, is not cited in the MRTP, does not support RJR's claims that snus will help smokers quit smoking or reduce cigarette consumption.

In the MRTP application, RJR states that data from the NIH/FDA's PATH study are "directionally consistent" with RJR's conclusion from their own study (CSD0904) "showing differences of up to 25%" in cigarettes smoked per day among dual-users of cigarettes and Camel Snus vs. exclusive cigarette smokers (Executive Summary, Page 142).

RJR does not provide any quantitative data from the PATH study to support this statement. In Module Section 3.5.2.2, RJR defines "current use" of Camel Snus in PATH as use in the past 30 days. *Examining the Adult Wave 1 Public Use Files from PATH, the "directionally consistent" conclusion does not apply to past 30-day dual-users of cigarettes and only snus.* There is no difference in cigarettes smoked per day between past 30-day exclusive cigarette smokers and past 30-day dual-users of cigarettes and snus alone, although very few respondents exhibited this behavior (N=19). The apparent reduction in cigarettes applies only if poly-users of multiple tobacco products are included in the snus category, and this difference is partly due to confounding: it shrinks after adjustment for age, sex, and race/ethnicity (Table 1).

⁹ Biener L, Roman AM, Mc Inerney SA, Bolcic-Jankovic D, Hatsukami DK, Loukas A, O'Connor RJ, Romito L. Snus use and rejection in the USA. *Tob Control*. 2016 Jul;25(4):386-92.

Table 1. Cigarettes Smoked Per Day Among Exclusive Cigarette Smokers and Cigarette Smokers Also Using Snus: no meaningful reduction in smoking after adjustment for socio-demographic variables.

	n	Cigarettes/day, Weighted Unadjusted	Cigarettes/day, Weighted Adjusted
Exclusive cigarettes	6812	16.7	16.6
Cigarettes + snus (any brand), including poly-use	222	14.5	16.6
Cigarettes + Camel Snus, including poly-use	53	13.0	15.3
Cigarettes + snus (any brand), dual-use only	19	16.6	18.0
Cigarettes + Camel Snus, dual-use only	5	17.2	-

Methods: PATH Wave 1 Adult Public Use File. Observations with complete data regarding past 30-day use of all tobacco products in the PATH survey (N=30,614). Dual-use refers to using only cigarettes and snus in the past 30 days. "Camel Snus" refers to those reporting Camel Snus as their usual or most recently used snus brand. Mean cigarettes per day refers to cigarettes smoked on days smoked for someday smokers and every day for daily smokers. Weighting by balanced repeated replication. Adjustment variables were sex (male, female), age (18-24, 25-34, 35-44, ≥45), and race/ethnicity (non-Hispanic white, non-Hispanic Black, non-Hispanic other, Hispanic). Adjusted marginal means obtained from Stata 14 "margin" command following fitting of weighted, adjusted negative binomial regression models for cigarettes per day (skewed outcome variable distribution). Too few observations (n=5) to obtain adjusted estimates in Camel Snus dual-use category; snus categories not mutually exclusive.

Also in PATH, the prevalence of snus use was not meaningfully different between individuals who had recently quit smoking cigarettes and current established cigarette smokers, suggesting that, as actually used in real world settings, very few cigarette smokers "switch completely" to snus (Table 2).

Table 2. Prevalence of Snus Use Among Current and Former Cigarette Smokers: snus use uncommon and not meaningfully greater among recent quitters and use is even lower among long-term quitters

	n	Weighted, Unadjusted		Weighted, Adjusted	
		Ever Used Snus, %	Currently Use Snus, %	Ever Used Snus, %	Currently Use Snus, %
Current Established Cigarette Smokers	11,342	13.8	1.2	11.1	0.9
Recent (<12 mo.) Cigarette Quitters	1086	14.4	1.6	11.7	1.2
Long-term (>12 mo.) Cigarette Quitters	3811	5.1	0.5	7.3	0.7

Methods: PATH Wave 1 Adult Public Use File. Observations with complete data regarding use of cigarettes and snus; Current established cigarette smoking (smoked >100 cigarettes and now

smokes every day or some days); Recent cigarette quitter (smoked >100 cigarettes, now does not smoke at all, last smoked within the past year); Long-term cigarette quitter (smoked >100 cigarettes, now does not smoke at all, last smoked >12 months ago), Currently use snus (has used snus "fairly regularly" and uses every day or some days); Weighting by balanced repeated replication. Adjustment variables were sex (male, female), age (18-24, 25-34, 35-44, ≥45), and race/ethnicity (non-Hispanic white, non-Hispanic Black, non-Hispanic other, Hispanic). Adjusted marginal means obtained from Stata 14 "margin" command following fitting of weighted, adjusted logistic regression models for outcomes ever or current snus use.

The PATH survey also asked current and former snus users to endorse their motivations to try or use snus. Using snus at times or in places where smoking is not allowed was endorsed more often (79.8%) than snus helps people quit cigarettes (37.4%) or than being less harmful to oneself (38.9%) or to others (55.4%). ***This shows that evading smoking restrictions, which would lead to population harm, is a greater motivation for using snus than is using snus for harm reduction.***

The Wave 1 PATH data, collected independently of the tobacco industry, suggest that using snus in combination with cigarettes: 1) is associated with minimal, if any, reduction in the mean number of cigarettes smoked per day; 2) is not associated with more cigarette quitting; and that 3) snus users are motivated to use snus to evade smoking restrictions. ***These findings are not consistent with harm reduction.***

Data from other large national surveys also demonstrate that use of snus among US adults is very low, indicating limited appeal overall, even among cigarette smokers.

- In a national study of 5,717 US adults in 2014, Weaver and colleagues found that only 4% of respondents reported ever trying snus and just 0.3% used currently.¹⁰
- In a national survey of 2,067 US adults in 2013, Kaufman and colleagues reported 5% prevalence of ever trying snus, with current use at <1%.¹¹
- In 2012, among a telephone survey of 3,627 US adults, current use of snus, either alone (0.1%) or with cigarettes (0.2%) was rare.¹²

Additional observational studies of snus use in the USA show that complete switching and smoking cessation have not been consumers' actual patterns of use.

Since RJR introduced snus into the U.S. market in 2006, consumers have been unlikely to switch completely to snus from cigarettes. A qualitative study of 65 smokers in California¹³ found that despite aggressive promotion and receiving free samples of Camel Snus,

¹⁰ Weaver SR, Majeed BA, Pechacek TF, Nyman AL, Gregory KR, Eriksen MP. Use of electronic nicotine delivery systems and other tobacco products among USA adults, 2014: results from a national survey. *Int J Public Health*. 2016 Mar;61(2):177-88.

¹¹ Kaufman AR, Mays D, Koblitz AR, Portnoy DB. Judgments, awareness, and the use of snus among adults in the United States. *Nicotine Tob Res*. 2014 Oct;16(10):1404-8.

¹² Lee YO, Hebert CJ, Nonnemaker JM, Kim AE. Multiple tobacco product use among adults in the United States: cigarettes, cigars, electronic cigarettes, hookah, smokeless tobacco, and snus. *Prev Med*. 2014 May;62:14-9.

- smokers found these products were not an acceptable temporary or permanent substitute for smoking.
- For some, using these products reinforced their preference for smoking.
- Snus was used intermittently in situations such as smoke-free environments or to avoid social stigma from smoking
- Few smokers were willing to continue using snus after trying a free sample, and none found it to be an acceptable substitute for smoking or a viable smoking cessation aid.

Another early observational study¹⁴ of 4067 adult smokers in 2008 following the introduction of snus into the US market found

- 29% of young adult males reported trying snus
- snus trial was negatively associated with intention to quit smoking
- snus trial was not associated with smoking cessation

A national study of 1836 current and recent former smokers in the USA¹⁵ in 2011 found

- smokers planning to quit in the next 6 months or unsuccessful quitters were the most interested in using alternative tobacco products, including snus
- younger, white, lower education and lower income smokers were more likely to have used snus
- snus use was not associated with smoking cessation

A national population-based survey¹⁶ of 12,400 smokers in the USA in 2010-2011 who had made a quit attempt in the past year found that

- switching to smokeless tobacco products (including snus) to quit was reported by 3.1% of smokers
- switchers were more likely to be male, white, younger, and to smoke within 30 minutes of waking
- attempting to switch to smokeless tobacco was not associated with successful smoking cessation

Even RJR's own studies demonstrate that consumers will likely use Camel Snus in conjunction with other tobacco products. In RJR's sponsored study (CSD0804, described in Section 3.5.2.1), adults who used Camel Snus were unlikely to be exclusive users of snus alone:

- Only 13% of the Camel Snus users in the study used only snus (87% of Camel snus users also used other tobacco products)
- More often, snus was used in dual-use with cigarettes (49%), with cigarettes and other tobacco products (30%), or with tobacco products other than cigarettes (8%)

¹³ Bahreinifar S, Sheon NM, Ling PM. Is snus the same as dip? Smokers' perceptions of new smokeless tobacco advertising. *Tob Control*. 2013 Mar;22(2):84-90.

¹⁴ Biener L, McCausland K, Curry L, Cullen J. Prevalence of trial of snus products among adult smokers. *Am J Public Health*. 2011 Oct;101(10):1874-6.

¹⁵ Popova L, Ling PM. Alternative tobacco product use and smoking cessation: a national study. *Am J Public Health*. 2013 May;103(5):923-30.

¹⁶ Schauer GL, Malarcher AM, Babb SD. Prevalence and correlates of switching to another tobacco product to quit smoking cigarettes. *Nicotine Tob Res*. 2015 May;17(5):622-7.

- The published version of this study¹⁷ reveals that only 53 participants were enrolled; recruitment procedures are not reported in sufficient detail to assess generalizability

In RJR's reports (Section 3.5.2.2.3), derived from the RAI-funded National Tobacco Behavior Monitor and RJR's Consumer Brand Tracker Survey, show that exclusive use of snus, as implied in RJR's proposed claim that smokers should *switch completely* to snus, is a rare behavior among actual snus consumers:

- Only 7% of Camel Snus users were exclusive snus users; dual- or poly-use of snus with cigarette or non-cigarettes combustibles and/or non-combustibles was, by far, the dominant use pattern.
- The Brand Tracker survey estimated an even lower prevalence of exclusive snus use among all snus users (3.5%). Exclusive use was less common with snus than with non-snus moist snuff (23%) or chewing tobacco (6%).

In RJR's clinical study CSD0904, "natural product adaptors" who had been using snus for at least 6 months were confined to a clinical facility to monitor their tobacco use. RJR reported that this study suggests that snus-cigarette dual-users smoke fewer cigarettes per day than cigarette-only smokers ("reductions up to 25%"), while also reporting that the clinical confinement conditions of the study resulted in "fewer opportunities to smoke because of required study procedures and access to designated smoking area" (Executive Summary page 134). Because of the confinement condition, it is unlikely that the observations in this study reflect real-world use patterns of snus and cigarettes. To our knowledge, the findings of this study have not been published, and the details are contained in Module 6, which has not been posted as of August 20, 2018.

RJR also conducted three "likelihood of use studies" to assess how consumers would respond to the proposed modified risk marketing advertisements and the level of interest in purchasing Camel Snus among smokers and non-smokers (see: Application Section 3.5.1.2). While RJR concluded that, "consumers are likely to comply with instructions for product use necessary to achieve the expected reduction in risk," the data to support this claim are in Section 6.3 of the application, which is not available to the public. It is not possible for the public to assess the adequacy of the methods or the appropriateness of this interpretation of the findings.

The MRTP application should not be approved without sufficient opportunity for the public to examine the contents of these two studies and the other material in Module 6.

Finally, an independent study of Air Force recruits in the year following Basic Training provides insight into the unlikely probability that smokeless tobacco will be used in a harm reduction context among US smokers.¹⁸ Although focused on conventional snuff and chewing tobacco (not snus), the study reported that harm reduction was uncommon (i.e., from smoking to smokeless

¹⁷ Caraway JW, Chen PX. Assessment of mouth-level exposure to tobacco constituents in U.S. snus consumers. *Nicotine Tob Res.* 2013 Mar;15(3):670-7.

¹⁸ Klesges RC, Sherrill-Mittleman D, Ebbert JO, Talcott GW, Debon M. Tobacco use harm reduction, elimination, and escalation in a large military cohort. *Am J Public Health.* 2010 Dec;100(12):2487-92.

use), but harm escalation (i.e., from smoking-only to dual-use or from smokeless-only to dual-use or smoking) was common. Specifically:

- Baseline cigarette-only smokers were more likely to add smokeless tobacco (become dual-users) than switch to use of smokeless tobacco only (5.6% vs. 0.9%)
- Baseline smokeless and cigarette dual-users were more likely to stay dual-users with cigarettes (25%) or switch to cigarette-only smoking (42%) than become smokeless-only users (12%)

These real-world findings indicate concern that harm escalation – not harm reduction -- will accompany the promotion of smokeless tobacco products for harm reduction.

The clinical trial and epidemiologic evidence presented above -- including RJR's own studies -- indicates that the most likely outcome of marketing Camel Snus with reduced harm claims will be no net change in smoking and perhaps depressed smoking cessation, with prolonged dual-use.

Implications for Modeling Population Effects

- Camel Snus has been available to US smokers for approximately 10 years, providing ample opportunity for smokers interested in harm reduction to switch to this product, and relatively few have done so: use is <1% among former smokers.¹⁹
- The number of additional smokers who switch completely to snus under the proposed marketing claims would need to *exceed* the number of smokers who have already switched or would switch under current marketing by an order of magnitude to reach the 14.2-16.5% switching probability used in RJR's Dynamic Population Model. This hypothetical switching probability is unrealistic given that:
 - RJR's own trial demonstrated that providing harm reduction information did not affect harm reduction behavior among cigarette smokers given Camel Snus²⁰
 - Most smokers do not perceive snus to be an appealing substitute for smoking²¹
- The clinical trial data indicate that snus products may depress quitting smoking among cigarette users,²² a major harm to population health that is omitted from RJR's calculations in the Dynamic Population Model.
- Less harmful, FDA-approved cessation strategies are already available to smokers; the proposed MRTP claims may discourage smokers from using them. Currently:
 - Most adult smokers (84%) believe using stop-smoking medications makes it easier to quit²³

¹⁹ Biener L, Roman AM, Mc Inerney SA, Bolcic-Jankovic D, Hatsukami DK, Loukas A, O'Connor RJ, Romito L. Snus use and rejection in the USA. *Tob Control*. 2016 Jul;25(4):386-92.

²⁰ Nelson PR, Chen P, Battista DR, Pillitteri JL, Shiffman S. Randomized Trial to Compare Smoking Cessation Rates of Snus, with and without Smokeless Tobacco Health-Related Information, and a Nicotine Lozenge. *Nicotine Tob Res*. 2018 Jan 24.

²¹ Meier E, Burris JL, Wahlquist A, Garrett-Mayer E, Gray KM, Alberg AJ, Cummings KM, Carpenter MJ. Perceptions of Snus Among US Adult Smokers Given Free Product. *Nicotine Tob Res*. 2017 Dec 13;20(1):22-29.

²² Carpenter MJ, Wahlquist AE, Burris JL, Gray KM, Garrett-Mayer E, Cummings KM, Alberg AJ. Snus undermines quit attempts but not abstinence: a randomised clinical trial among US smokers. *Tob Control*. 2017 Mar;26(2):202-209.

- The main barriers to use of NRT are not that smokers find these treatments to be unacceptable, but rather include limited knowledge, poor technique of use, and lack of role models using NRT successfully²⁴
- In all studies above, switching completely to snus was far less common than dual use of snus with cigarettes, and dual use was not associated with a significant reduction in number of cigarettes smoked, substantially diminishing any harm reduction benefit.

The available evidence does not support RJR's claim that marketing snus with modified risk claims would confer benefit at the population level. In contrast, such marketing could do harm. This MRTP application should be denied.

²³ Bondy SJ, Diemert LM, Victor JC, McDonald PW, Cohen JE. Assessing the reach of nicotine replacement therapy as a preventive public health measure. *Chronic Dis Inj Can*. 2012 Dec;33(1):19-28.

²⁴ Herbec A, Tombor I, Shahab L, West R. "If I'd Known ..." -a Theory-Informed Systematic Analysis of Missed Opportunities in Optimising Use of Nicotine Replacement Therapy and Accessing Relevant Support: a Qualitative Study. *Int J Behav Med*. 2018 Jul 30. doi: 10.1007/s12529-018-9735-y.