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Tobacco Products Scientific Advisory Committee
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RE: Modified Risk Tobacco Product Applications: Applications for Six Camel Snus Smokeless Tobacco Products Submitted by R.J. Reynolds Tobacco Company. Docket Number: FDA-2017-N-4678-0001

Dear Members of TPSAC:

R.J. Reynolds (RJR) is seeking Modified Risk Tobacco Product (MRTP) orders for six Camel Snus smokeless tobacco products: Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, and Camel Snus Winterchill. RJR proposed three different modified risk advertising executions for each of the six Camel Snus styles, and thus requested a total of 18 MRTP orders. FDA has asked TPSAC for its assessment of this application.

To be granted a MRTP order, Section 911(g) of the Family Smoking Prevention and Tobacco Control Act (TCA) places the burden on RJR to present sufficient scientific evidence to demonstrate that Camel Snus, *as actually used by consumers*, will *both:*

(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, including users and current non-users of tobacco products.

It is important to recognize that RJR must meet *both* requirements stated in the statute; it is necessary but not sufficient, for RJR only to show that Camel Snus use is less likely to cause lung cancer, oral cancer, respiratory disease, or heart disease in individual users. Rather, RJR must demonstrate that marketing Camel Snus as an MRTP will benefit the public health, which includes considering dual use with cigarettes and other tobacco products as well as effects on tobacco initiation and cessation. In addition, RJR must demonstrate that the proposed advertising and labeling will enable the public to comprehend the information concerning modified risk in the context of total health.

UCSF has submitted five public comments (summarized in detail in the Appendix to this letter) that show that RJR has not met this burden and, indeed, that a careful reading of the material in their MRTP application suggests that the proposed marketing of Camel Snus could harm public health.

1. The premise and essential condition for all three of RJR's MRTP claims is that smokers "switch completely" from cigarettes to Camel Snus. However, the evidence RJR presents as well as the independent scientific literature shows that, *as actually used by consumers*, current smokers are

unlikely to switch completely to snus, but instead are more likely to follow a pattern of dual- or poly-use. Most Camel Snus users will continue to use cigarettes and/or other tobacco products at the same time that they use snus.

2. Camel Snus, even used alone, may increase users' exposure to some dangerous toxicants and therefore increase, rather than reduce, risks of some tobacco-induced diseases even if it lowers risks of others. Using Camel Snus in combination with cigarettes, the most likely use pattern, will increase, rather than reduce, health harms to individuals.
3. Current cigarette smokers who also use Camel Snus (the most likely use pattern) are less likely to quit smoking, and MRTP claims are likely to encourage smokers who would otherwise quit to simply add Camel Snus.
4. MRTP claims are likely to increase Camel Snus uptake among tobacco non-users, especially youth and adolescents, a point RJR does not address in its MRTP application. The flavored Camel Snus products are even more likely to attract youth and adolescents than unflavored products.
5. Youth who initiate smokeless tobacco use through Camel Snus are at increased risk of subsequently smoking cigarettes (i.e., the "gateway effect"), a reality RJR dismisses.
6. The actual evidence in RJR's MRTP application contradicts the presumption that Camel Snus assists cessation, but rather shows that snus is no better than nicotine gum as a cigarette substitute, is less appealing, is more toxic, and is associated with higher rates of prolonged use.
7. RJR did not use appropriate experimental methods that permit drawing RJR's conclusion that consumers would understand the proposed Camel Snus advertisements

Because RJR failed to demonstrate that marketing Camel Snus with modified risk claims will, as actually used by consumers, both significantly reduce risks and benefit the health of the population as a whole, TPSAC should recommend that FDA not issue a MRTP order to RJR for Camel Snus.

Finally, as of August 22, 2018, FDA had still not posted the entire Camel Snus MRTP application materials. Key materials that are not yet available to the public include Module 6, Summary of All Research Findings; Module 7.2, In vivo Scientific Studies and Analyses; complete list of references; amendments. The unavailability of these key scientific materials precludes a complete scientific review and analysis of the MRTP application. As a result, TPSAC does not have the full benefit of public comment needed to aid in TPSAC's statutorily mandated review of and preparation of recommendations concerning RJR's MRTP application for Camel Snus.

Thank you for your consideration.

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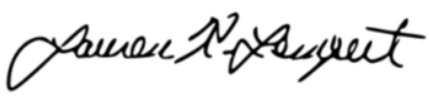

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APPENDIX: Detailed Summary of UCSF TCORS COMMENTS

1. **Epidemiology and Use Patterns (Benjamin Chaffee et al.)**
   a. Current combustible tobacco users are unlikely to switch completely to Camel Snus; the most probable pattern of Camel Snus use will be dual use.
   b. RJR's and independent scientific trials do not support the presumption that Camel Snus use would increase cessation, or are more effective than FDA-approved cessation products.
   c. Reynolds America Inc.'s study does not support RJR's contention that Camel Snus will assist smokers in quitting or in reducing cigarettes smoked, even with reduced risk claims.
   d. Marketing Camel Snus with reduced harm claims may depress smoking cessation.
   e. Marketing Camel Snus with MRTP claims would not confer benefit at the population level, and may increase harm.

2. **Toxicity (Gideon St. Helen et al.)**
   a. RJR's own studies show that, rather than reducing levels of exposure, users of Camel Snus are exposed to greater levels of some dangerous toxicants, including nitrosamines (NNN and NNK) and heavy metals (cadmium, and arsenic).
   b. Contrary to RJR's claims, Camel Snus has considerably higher levels of NNN and NNK compared to at least one other major U.S. brand of snus as well as Swedish snus.
   c. Since most users of Camel Snus will likely be smoking cigarettes concurrently, their exposure to dangerous toxicants would increase their risk of several tobacco-related diseases.
   d. RJR does not present sufficient evidence in its chemistry studies to support their claim that Camel Snus users will reduce their exposure to toxicants in a way that will generally reduce their risk of harm of tobacco-related diseases, and may in fact increase their risk of other diseases.

3. **Youth (Bonnie Halpern-Felsher et al.)**
   a. RJR does not consider the appeal to or impact of Camel Snus and its marketing claims on youth or adolescents.
   b. RJR's does not consider the likelihood that youth or adolescents will misperceive the risks of Camel Snus.
   c. RJR does not consider whether Camel Snus will result in initiation among non-users, or in dual or poly-use.
   d. RJR fails to consider the role that flavored Camel Snus will have on youth.
   e. RJR did not meet its burden to demonstrate that Camel Snus, as actually used by consumers, will benefit the health of the population as a whole, especially taking into account youth, adolescents, and other non-users.

4. **Marketing and Communications (Lucy Popova et al.)**
   a. RJR's "Consumer Comprehension and Persuasion" studies did not use randomized experimental design and, therefore, do not demonstrate how the advertisement materials affected understanding and consumer comprehension.
   b. Contrary to RJR's claims, their proposed Camel Snus modified risk advertising materials do not "further educate smokers about the risks of cigarette smoking."
   c. RJR presents an incomplete literature to support their claim that consumers overestimate risks of smokeless tobacco compared to cigarettes and ignores relevant papers that contradict their position.
   d. The Executive Summary in RJR's MRTP application misrepresents RJR's own findings. In particular, the executive summary claims that advertisements did not increase interest among smokers who are likely to quit, but the reports for actual studies demonstrate that advertisements increased interest in both smokers who are and are not likely to quit.

e. RJR's "likelihood of use" studies selectively asked some questions of smokers with and without quitting intentions in a way that obfuscates the effects of these advertisements on different groups. Among smokers without quitting intentions, after seeing the modified risk advertisements, only 14-22% envisioned using snus instead of smoking, while 30%-34% would replace some cigarettes with snus and 20%-23% would add snus use on top of smoking, increasing their overall tobacco use. This question was not asked of smokers with quitting intentions.
f. RJR's MRTP application did not demonstrate that its marketing would effectively communicate scientifically accurate statements in a way that would accurately impact consumer understanding and perceptions.

5. Population Health Model (Wendy Max et al.)

a. RJR's Dynamic Population Modeler (DPM (+1)), a statistical model RJR uses to forecast the population effect of Camel Snus, is biased in favor of finding a population health benefit.
b. Contrary to FDA's Guidance, the DPM (+1) model only considers mortality while ignoring morbidity.
c. RJR acknowledges that they omit the possibility that snus use may delay smoking cessation, which would increase smoking-attributable mortality and decrease the public health benefit.
d. The model does not consider the potential additive effect of dual- and poly-use.
e. The model does not use the most recent data on smoking initiation or cessation.
f. The model does not include the impact of Camel Snus use on non-tobacco users.
g. The model's assumptions that switching rates (from cigarette to Camel Snus) are much greater than initiation rates (from never tobacco users to Camel Snus) bias the results.
h. The model does not consider people who may switch from e-cigarettes to Camel Snus.
i. Because of some unsupported assumptions, the negative impact of the gateway effect whereby youth initiate tobacco use with snus and progress to cigarettes is probably underestimated in the model.
j. The model's estimates of the excess relative risk of smoking vs snus use are low and not based on empirical evidence and bias the findings on population health impact.
k. The data used for validation of the DPM (+1) are problematic.
l. The sensitivity analyses are incomplete and bias the conclusions designed to favor a positive impact on population health.
m. RJR has not convincingly demonstrated that Camel Snus will benefit the health of the population as a whole.
n. Because the DPM (+1) is biased in favor for finding a population health benefit for marketing Camel Snus with MRTP claims, FDA should not rely on the model results as presented by RJR.

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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 Act[1] and FDA's Guidance for Industry on Modified Risk Tobacco Product (MRTP) Applications[2] (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 received 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]

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[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 MRTP 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 assessment[8]).
- 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

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[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

		Weighted, Unadjusted		Weighted, Adjusted	
	n	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 California[13] 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 study[14] 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 USA[15] 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 survey[16] 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%)

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[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 study[17] 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 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 Snus[20]
    - Most smokers do not perceive snus to be an appealing substitute for smoking[21]
- 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 quit[23]

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[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 successfully[24]
- 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.

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

Reynolds' own data do not support their claim that because exclusive users of Camel Snus experience lower levels of exposure to some toxicants, they will reduce their risk of harm from lung cancer, oral cancer, respiratory disease, and heart disease

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RJ Reynolds Tobacco Company (Reynolds) seeks risk modification orders under the Family Smoking Prevention and Tobacco Control Act (TCA) Section 911(g)(1) for six Camel Snus products (Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, and Camel Snus Winterchill). In its modified risk tobacco product application (MRTP), Reynolds seeks to demonstrate that the results of its own studies on the six Camel Snus products, combined with the body of U.S. smokeless tobacco epidemiology studies, human clinical studies, preclinical toxicology studies, and chemistry studies, provide sufficient scientific basis to conclude that, for individuals who are current cigarette smokers, switching completely from smoking cigarettes to Camel Snus can significantly or greatly reduce those individual's risk for lung cancer, oral cancer, respiratory disease, and heart disease. Additionally, Reynolds seeks to demonstrate that an MRTP order will benefit the population as a whole, taking into account both users and current non-users of tobacco products.

At the core of Reynolds' reduced risk claim is the argument that smokers who switch completely to Camel Snus reduce their health risks for two principal reasons: (1) Camel Snus toxicant content is comparable to, or less than, the historical U.S. and Swedish smokeless tobacco products on which epidemiological studies are based, and (2) Camel Snus usage patterns suggest lower levels of toxicant exposure compared to the historical patterns reflected in U.S. and Swedish epidemiology. (Executive Summary, pp. 78-79) In other words, Reynolds appears to argue that because exclusive users of Camel Snus experience lower levels of exposure to some toxicants, these exclusive users of Camel Snus will have reduced risk of harm from lung cancer, oral cancer, respiratory disease, and heart disease. In this comment, we focus on the sufficiency of the evidence Reynolds submitted in its chemistry studies to support this claim. We show that Reynolds' own studies show that, rather than reducing levels of exposure, users of Camel Snus are in fact exposed to greater levels of some dangerous toxicants, including NNN, NNK, cadmium, and arsenic. Moreover, Reynolds' argument is based on the premise that users will "switch completely" from cigarette smoking to Camel Snus. However, studies have shown that most users of smokeless tobacco products are dual users. Therefore, most users of Camel Snus will likely also be smoking cigarettes concurrently, which would actually increase their exposure to these dangerous toxicants and would thereby increase their risk of several tobacco-related diseases.

TCA Section 911(g)(1) requires Reynolds to demonstrate that Camel Snus, "*as it is actually used by consumers"*, will (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." (Emphasis added.) It is essential that Reynolds meet all parts of this statutory

mandate, and the studies Reynolds relies on must be based on how the product is *actually used by consumers.* Therefore, as a preliminary matter, Reynolds' scientific studies must acknowledge that most users of smokeless tobacco products (including Snus) are dual users, and FDA must address whether Reynolds has demonstrated that Camel Snus users will completely switch from smoking cigarettes to using Camel Snus. Studies conducted or financed by Reynolds and cited in its MRTP application show that dual or poly-use with cigarettes or other tobacco products is the predominant use pattern among snus users (CSD0804: 13% exclusive snus use; 87% dual or poly use; National Tobacco Behavior Monitor: 7% exclusive snus use; 93% dual or poly use; Brand Tracker Survey: 3.5% exclusive use; 96.5% dual or poly use). Published studies conducted independent of the tobacco industry also show dual and poly use to be the dominant snus use pattern.[1] If Reynolds failed to demonstrate that snus users will switch completely with sufficient scientific evidence, then Reynolds' studies must consider the increased toxicant exposure and concomitant increased health risks that would affect individuals who smoke cigarettes concurrently while using Camel Snus.

Reynolds downplays their own findings of higher nitrosamine and heavy metal levels in Camel snus compared to tobacco smoke

Reynolds' own data, as summarized in the Executive Summary of their MRTP application, show that Camel Snus does not meet the legal standard for making a reduced risk claim, and should not be marketed as a modified risk tobacco product. On page 187 of the Executive Summary, Reynolds makes the statement that "cigarette smoke is far more chemically complex than smokeless tobacco and contains many more FDA-designated and reportable HPHCs" (HPHCs, harmful and potentially harmful constituents). This is true, since tobacco smoke contains thousands of chemical products of pyrolysis and combustion reactions that are absent or, if present, are at lower levels in smokeless tobacco products. More important, Reynolds states on page 189 of the Executive Summary that "Camel Snus contains lower levels of some HPHCs and ***greater amounts of others*** relative to tobacco smoke." This admission by Reynolds is significant and is critical to the assessment of whether Camel Snus is a reduced harm product. As will be discussed below, tobacco-specific nitrosamine (TSNA) levels are higher in smokeless tobacco than tobacco smoke and systemic exposure to TSNAs from smokeless tobacco use can exceed that of cigarette smokers.[2] One such TSNA, NNK, a potent pulmonary carcinogen, can induce lung tumors in rodents, ***independent of route of administration***,[3] suggesting that reduced risk claims, including lung cancer, for Camel Snus are questionable and FDA should not approve these claims.

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[1] 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.
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.

[2]Benowitz NL, Renner C, Lanier A, Tyndale RF, Hatsukami DK, Lindgren BR, Stepanov I, Watson CH, Sosnoff C, Jacob P. Exposure to nicotine and carcinogens among South Western Alaskan Native cigarette smokers and smokeless tobacco user. Cancer Epidemiology and Prevention Biomarkers. 2012:cebp. 1178.2011.
IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless tobacco and some tobacco-specific N-nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2007;89:1–592.

[3] Hecht, Stephen S., and Dietrich Hoffmann. "Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke." Carcinogenesis 9.6 (1988): 875-884.
Rivenson, Abraham, et al. "Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and Areca-derived N-nitrosamines." Cancer Research 48.23 (1988): 6912-6917.

The constituents that Reynolds have identified at higher levels in Camel Snus compared to tobacco smoke are tobacco-specific nitrosamines, such as NNN and NNK, the heavy metals, arsenic and cadmium, and nicotine (Table 2.9.5-3, Executive Summary p. 190). NNN and NNK are human carcinogens linked to esophageal cancer[4] and lung cancer[5], respectively. Heavy metals, such as cadmium and arsenic, contribute to cancer and cardiopulmonary disease, with greater contribution to cancer and non-cancer risk than tobacco-specific nitrosamines.[6] Higher levels of NNK, NNN, and heavy metals in Camel Snus compared to tobacco smoke contradicts the idea that Camel Snus is a reduced risk product, and may in fact present similar or higher risks for diseases related to these four constituents relative to tobacco smoke. Reynolds argues that "product chemistry data are not a measure of actual toxicant exposure when consumers use a tobacco product." (Exec. Summary p. 190) Rather, "Camel Snus users are exposed to only a fraction of the TSNAs and nicotine present in Camel Snus under actual conditions of use." (Exec. Summary p. 191) While we agree that users of tobacco products are exposed to a fraction of the constituents in that product (this is true for all products and constituents – smokers typically breath in 1 mg of nicotine from a cigarette stick containing 10-14 mg of nicotine[7]), we strongly disagree with Reynolds downplaying the importance of product chemistry to systemic exposure and health risks. Systemic exposure to tobacco toxicants is a function of the chemistry of the products, constituent delivery and bioavailability, and user characteristics (use patterns). In assessing potential health risks of tobacco products, the importance of these individual factors should not be minimized. Users of smokeless tobacco products in the U.S. have higher intake of NNK precisely because the NNK levels are typically higher in smokeless tobacco products in the U.S. than in cigarette smoke, as Reynolds' own data support. Of further concern, under "actual conditions of use," most Camel Snus users will likely continue to smoke cigarettes, rather than "switch completely" to Camel Snus.[8] Even if they reduce their cigarette consumption, they will still be exposed to substantial amounts of both smokeless tobacco toxicants and smoke toxicants.

Reynolds claims on page 191 of the Executive Summary that Camel Snus has comparable or lower levels of HPHCs relative to other smokeless tobacco products sold in the U.S. That statement is not accurate. An independent study showed that Camel Snus products had ***higher NNN and NNK*** normalized by dry weight than Marlboro Snus products.[9] The NNN in Camel Snus ranged from 0.86-1.28 ug/g compared to a range of 0.42-0.47 ug/g in Marlboro Snus. Similarly, the NNK in Camel Snus ranged from 0.40-0.61 ug/g compared to 0.13-0.16 ug/g in Marlboro Snus. Further, Camel Snus contains higher levels of tobacco-specific nitrosamines

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[4] Yuan, Jian-Min, et al. "Urinary levels of the tobacco-specific carcinogen N′-nitrosonornicotine and its glucuronide are strongly associated with esophageal cancer risk in smokers." Carcinogenesis 32.9 (2011): 1366-1371.

[5] Hecht, Stephen S. "Tobacco smoke carcinogens and lung cancer." JNCI: Journal of the National Cancer Institute 91.14 (1999): 1194-1210.

[6] Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tob Control 2003;12(4):424-430.

[7] Hukkanen J, Jacob III P, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacological Reviews. 2005;57(1):79-115.

[8] Tomar, Scott L., Hillel R. Alpert, and Greg N. Connolly. "Patterns of dual use of cigarettes and smokeless tobacco among US males: findings from national surveys." Tobacco Control (2009): tc-2009.
Rath, Jessica M., et al. "Patterns of tobacco use and dual use in US young adults: the missing link between youth prevention and adult cessation." Journal of environmental and public health 2012 (2012).

[9] Stepanov, Irina, et al. "Monitoring tobacco-specific N-nitrosamines and nicotine in novel Marlboro and Camel smokeless tobacco products: findings from Round 1 of the New Product Watch." Nicotine & Tobacco Research 14.3 (2011): 274-281.

compared to Swedish Snus.[10] Also, an internal 2007 document from Reynolds reported higher cadmium and chromium in Camel Snus compared to Swedish Snus.[11]

In summary, Reynolds' own data show that Camel Snus has higher levels of nitrosamines and heavy metals compared to tobacco smoke and FDA should not overlook these results. Further, contrary to Reynolds' statement, Camel Snus has considerably higher levels of NNN and NNK compared to at least one other major US brand of Snus as well as Swedish Snus.

Reynolds conducted human studies of exclusive Camel Snus use, dual use, and switching to examine systemic exposure to various HPHCs using biomarkers. Reynolds reported that Camel Snus results in "lower exposure to combustion-related compounds in exclusive users." Biomarkers of polycyclic aromatic hydrocarbons (PAHs), phenanthrene and fluorene, were lower following exclusive Camel Snus use compared to smoking while biomarkers of other PAHs, pyrene and naphthalene, were comparable to smoking. To explain the comparable levels of pyrene and naphthalene between Camel Snus and tobacco smoking, Reynolds argues that these two PAHs are not specific to tobacco and can be affected by environmental exposures and genetics. Reynolds used one of our studies to support this explanation,[12] but our findings do not support this conclusion. While in general, PAHs are not specific to tobacco, we found that metabolites of fluorene and naphthalene (lighter molecular weight PAHs) are more specific to tobacco smoke and pyrene and phenanthrene are less specific. Our study suggested that while naphthalene can be produced from other sources, biomarkers of naphthalene were highly selective of tobacco smoke. Biomarkers of naphthalene measured after smoking likely originate from smoking. For this reason, the comparable levels of biomarkers of naphthalene during Camel Snus use and smoking that Reynolds reported indicate that Camel Snus may be a source of naphthalene. While we agree that there are other contributing sources of PAHs, ***it is likely that PAHs are present in Camel Snus as contaminants,[13] derived during the flue curing of tobacco. This is particularly relevant to heavier, less volatile PAHs, which are likely to be more carcinogenic.***

Regarding tobacco-specific nitrosamines (TSNA), Reynolds states that "Camel Snus use results in either similar or reduced exposure to toxicants present in tobacco when compared to exclusive cigarette smoking" (Executive Summary, p 138). Importantly, Reynolds states that their own sponsored study found "urinary levels of NNN, NAT, NAB and NNAL to be similar between exclusive Camel Snus users and cigarette smokers." To explain why Camel Snus use resulted in comparable PAH and TSNA biomarker levels to smoking, Reynolds argued that smoking decreased during confinement while Camel Snus use was consistent. "Opportunities to smoke while in-clinic were limited by study procedures and requirements to smoke inside a designated area. As such, these levels reflect less exposure from cigarettes than would be expected when smoking ad libitum outside the clinic…. Camel Snus users used consistent

[10] Stepanov, Irina, et al. "Tobacco-specific nitrosamines in new tobacco products." Nicotine & Tobacco Research 8.2 (2006): 309-313.

[11] https://www.industrydocumentslibrary.ucsf.edu/tobacco/docs/#id=zpcn0191

[12] St.Helen G, Goniewicz ML, Dempsey D, et al. Exposure and kinetics of polycyclic aromatic hydrocarbons (PAHs) in cigarette smokers. Chem Res Toxicol 2012;25(4):952-964

[13] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless tobacco and some tobacco-specific N-nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2007;89:1–592.

amounts of product both before and during clinical confinement. Therefore, these results likely under-represent differences in exposure between the two groups." (Executive Summary, p 138)

This argument by Reynolds should not be allowed to stand. Reynolds' own data show that levels of TSNAs in Camel Snus were higher than in cigarette smoke (Table 2.9.5-3, Executive Summary p. 190). Therefore, human studies showing similar TSNA biomarker levels from use of Camel Snus compared to smoking are not surprising and are consistent with independent studies showing similar levels of NNK biomarkers in smokers and smokeless tobacco users.[14] Further, cigarette smokers are known to titrate their desired nicotine dose by changing their smoking behavior and maintain a constant daily nicotine intake.[15] If participants reduced their cigarette consumption during the study, it is unlikely that biomarker levels would decrease significantly unless the reduction in consumption was dramatic. Reynolds gave no evidence of a dramatic decrease in number of cigarettes smoked by participants in the study.

On page 138 of the Executive Summary, Reynolds claims that the "TSNA biomarker results … demonstrate that exclusive Camel Snus users exhibit reduced or similar levels of these compounds when compared with cigarette smokers." It must be emphasized that similar levels of TSNAs from smokeless tobacco use compared to cigarette smoke in no way indicates that Camel Snus is a reduced risk product. Moreover, in addition to demonstrating that Camel Snus products will benefit the health of the population as a whole, TCA section 911(g)(1) requires Reynolds to demonstrate that the product, as it is actually used by consumers, will "***significantly reduce harm*** and the risk of tobacco-related disease to individual tobacco users." FDA's 2012 Guidance for Industry on Modified Risk Tobacco Product Applications (pp. 17-18) says, "An MRTPA must provide scientific evidence regarding the effect of the product on the health of individuals so that FDA can determine whether the MRTP does, in fact, modify risk as claimed by the applicant… In the case of an application for a risk modification order, the MRTPA must provide scientific evidence to demonstrate that the product significantly reduces harm and the risk of tobacco-related disease to individual users." Even if Reynolds showed that Camel Snus users are exposed to lower levels of some toxicants found in cigarette smoke, which is turn resulted in a *somewhat lower* overall risk compared with cigarettes, FDA must not issue a MRTP order unless Reynolds demonstrated that, as actually used by consumers, Camel Snus will result in a *significant reduction* in harm and the risk of tobacco-related disease.

On page 158 of the Executive Summary, Reynolds states, "Because Camel Snus is consumed orally, exclusive use of Camel Snus eliminates the direct exposure of lung tissues to toxicants, thereby mitigating some of the potentially harmful effects of those compounds experienced by cigarette smokers." This statement is troubling. As said before, NNK, the lung carcinogen, can induce lung tumors in rodents ***independent of route of administration***.[16] It is also notable that one of Reynolds' three advertising executions claims that Camel Snus reduces

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[14] Hecht, Stephen S., et al. "Similar exposure to a tobacco-specific carcinogen in smokeless tobacco users and cigarette smokers." Cancer Epidemiology and Prevention Biomarkers 16.8 (2007): 1567-1572.

[15] Ashton, Heather, R. Stepney, and J. W. Thompson. "Self-titration by cigarette smokers." Br Med J 2.6186 (1979): 357-360.

Herning, Ronald I., et al. "How a cigarette is smoked determines blood nicotine levels." Clinical Pharmacology & Therapeutics 33.1 (1983): 84-90.

[16] Hecht, Stephen S., and Dietrich Hoffmann. "Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke." Carcinogenesis 9.6 (1988): 875-884.

Rivenson, Abraham, et al. "Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and Areca-derived N-nitrosamines." Cancer Research 48.23 (1988): 6912-6917.

the risk of lung cancer and respiratory disease, but not the risk of oral cancer or heart disease. This suggests that Reynolds is aware that it did not present sufficient scientific evidence to support its claim that Camel Snus reduces the risk of oral cancer or heart disease. In the event that FDA issues a MRTP order based on any of the three advertising executions, FDA should consider requiring additional disclosures on Camel Snus labels pursuant to TCA section 911(h)(3)(A) and in their marketing claims that use of Camel Snus can increase the risk of certain tobacco-related diseases, including pancreatic cancer, X, Y, and Z. Additionally, pursuant to TCA section 911(h)(3)(B), FDA should consider requiring Reynolds to disclose on Camel Snus labels that any reduced risk is conditioned on using Camel Snus exclusively and not at the same time as other tobacco products.

In summary, based on findings of comparable levels of biomarkers of some PAHs and TSNAs from Camel Snus use relative to smoking, Reynolds' own data do not support their claim that because exclusive users of Camel Snus experience lower levels of exposure to some toxicants, these exclusive users of Camel Snus will reduce their risk of harm from lung cancer, oral cancer, respiratory disease, and heart disease. Additionally, Reynolds' cited studies fail to recognize that smokeless tobacco products like Camel Snus are rarely used exclusively; rather, smokeless tobacco products are typically used concurrently with cigarettes and/or other tobacco products.

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

R.J. Reynolds Tobacco Company's Application for Six Camel SNUS Smokeless Tobacco Minimizes its Appeal to Adolescents and the Likelihood that Youth and Adolescents Will Initiate Smokeless Tobacco or Smokeless Tobacco with Other Products

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RJ Reynolds Tobacco Company's (RJR) Modified Risk Tobacco Product (MRTP) application for Six Camel Snus smokeless tobacco products does not adequately consider the appeal or impact the product and its related claims can have on youth or adolescents, including whether and to what extent their products will result in youth misperceptions about the product risks, and whether their snus will result in initiation among non-users, and dual or poly-use. Further, their MRTP application fails to consider the role that their flavored products will have on youth. Therefore, the FDA should deny RJR's MRTP application for their six camel snus products.

On December 18, 2017, FDA filed for substantive scientific review of six RJ Reynolds Tobacco Company's (RJRT) Modified Risk Tobacco Product (MRTP) Applications for the following six varieties of its Camel Snus smokeless tobacco products: Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust Camel Snus Winterchill. RJR requests that the U.S. Food and Drug Administration issue orders authorizing RJR to advertise each of its Camel Snus styles (Frost, Frost Large, Winterchill, Robust, Mellow, and Mint, collectively, "Camel Snus") as a modified risk tobacco product ("MRTP") pursuant to Section 911 of The Family Smoking Prevention and Tobacco Control Act ("the TCA"). RJR proposes three different modified risk advertising executions for each of the six Camel Snus styles and is requesting a total of eighteen (18) MRTP orders.

Section 911 of the Family Smoking Prevention and Tobacco Control Act[1] and FDA's Guidance for Industry on Modified Risk Tobacco Product (MRTP) Applications[2] spell out the rigorous requirements that MRTP applicants must meet before a product can be deemed a "modified risk tobacco product" and can be marketed with MRTP claims. In particular, to market Snus with the MRTP claims stated above, RJR must prove 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.

In fulfilling the MRTP application requirements specified in section 911(g), FDA recommends in its MRTP Guidance that applicants submit, among other things, the following data and information:

[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

1) Scientific evidence regarding the effect that tobacco products and its marketing will have on increasing the likelihood that *non-users* (including never users and former users) will start using the product (Guidance, p. 20);
2) Data and information on how consumers *actually use* the product, including data and information addressing concurrent use of multiple products containing nicotine or tobacco (Guidance, p. 15), and scientific evidence demonstrating that consumers actually use the product in a way that exposes them to the claimed reduced level of substances or harm (Guidance, p. 17);
3) Human studies that evaluate consumer understanding and perceptions of the product, including its labeling, marketing, and advertising, including:

    a. The ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health;
    b. Consumers' beliefs about the health risks of using the product relative to other tobacco products;
    c. Consumer beliefs about the health risks of using the product relative to cessation aids; and
    d. Consumer beliefs about the risks of using the product relative to quitting all tobacco use (Guidance, pp. 20-21)

RJR has not met these criteria because the data necessary to support this claim are lacking or are presented in a way that is misleading. In addition, the proposed Camel Snus marketing is likely to appeal to tobacco non-users, including youth, something that RJR also ignores.

For these reasons, and others explained more fully below, FDA should deny RJR's MRTP application.

<u>The proposed Camel Snus marketing is likely to appeal to tobacco non-users, including youth</u>.

Because RJR's application did not consider the impact of Snus 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 Snus and its marketing would have on increasing the likelihood that adolescents who are currently not tobacco users will start using Snus.

Despite section 911(g)'s requirement, RJR failed to provide adequate scientific evidence demonstrating that their Snus 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.

In their application RJR argued that there is no evidence for a gateway effect; that is, that there is no evidence that those who use smokeless tobacco will subsequently use cigarettes or other tobacco products. However, the application's executive summary (pages 205-206 and 208) not only includes multiple prospective studies that demonstrate this association,[3] the application also fails to include a number of additional studies demonstrating that youth who use smokeless tobacco are more likely to smoke cigarettes in the future.[4]

[3] Severson, H. H., Forrester, K. K., & Biglan, A. (2007). Use of smokeless tobacco is a risk factor for cigarette smoking. Nicotine Tob Res, 9(12), 1331-1337.
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.
Joffer J, Burell G, Bergström E, Stenlund H, Sjörs L, Jerdén L. Predictors of smoking among Swedish adolescents. BMC Public Health. 2014 Dec 17;14:1296.
Taylor N, Choi K, Forster J. Snus use and smoking behaviors: preliminary findings from a prospective cohort study among US Midwest young adults. Am J Public Health. 2015 Apr;105(4):683-5.
[4] Walsh MM, Langer TJ, Kavanagh N, Mansell C, MacDougal W, Kavanagh C, Gansky. Smokeless tobacco cessation cluster randomized trial with rural high school males: intervention interaction with baseline smoking. Nicotine Tob Res. 2010 Jun;12(6):543-50.

Furthermore, RJR cites a number of studies that they conclude demonstrate a "reverse gateway" effect of smokeless tobacco, because youth who initiate tobacco use with cigarettes have been shown to be more likely to smoke cigarettes at follow-up than youth who initiate with smokeless tobacco.[5] This conclusion ignores the self-evident fact that youth who initiate tobacco use with cigarettes *are already smoking cigarettes*, and therefore are not an appropriate comparison group for calculating the onset of smoking among youth. Clearly, youth who have already smoked are the risk-group most likely to continue smoking. RJR uses this apples-to-oranges comparison with the "positive gateway" studies to dismiss completely the consistent, positive, prospective association between smokeless tobacco use among youth who have never smoked and subsequent onset of cigarette smoking.

RJR's application did not include information from studies with adolescents younger than 18

RJR did not provide any reliable information in its application on whether adolescents would be interested in using Snus, if adolescents would initiate nicotine/tobacco use with Snus, if adolescents would switch from another tobacco product to Snus, or if adolescents would use Snus along with other tobacco products.

One way to obtain information on adolescents' interests and behavior is to conduct studies with adolescents. However, neither RJR nor any other 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 conducted with no direct or indirect involvement of tobacco companies or their agents.[6]

The available evidence reported in scientific studies on currently marketed novel tobacco products conducted independent of the tobacco industry indicates that the introduction of novel products will attract adolescent non-users into initiating use. Adolescents' decisions to adopt use of any tobacco product are based on several considerations, including whether the product appeals to them, the product's flavors, smell and taste, the product's perceived harm reduction, and the ease and location of use.[7] The marketing of Snus with harm reduction claims and the claim that they are "smokeless" makes it likely that these products will appeal to youth.

Concern that individuals "misperceive" the relative harms of cigarettes and smokeless tobacco is overstated.

On page 84, the executive summary states, "In developing modified risk advertising, RJR was acutely aware of the prevailing public misperception that use of smokeless tobacco, including snus, is at least as harmful as cigarette smoking. Studies that have evaluated consumer perceptions show that, contrary to the consensus in the public health and tobacco control communities, the public (including consumers) believes – erroneously – that smokeless tobacco products are as harmful as, or more harmful than, cigarettes."

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; Ary DV, Lichtenstein E, Severson HH. Smokeless tobacco use among male adolescents: patterns, correlates, predictors, and the use of other drugs. Prev Med. 1987 May;16(3):385-401.

[5] Rodu B, Cole P. Evidence against a gateway from smokeless tobacco use to smoking. Nicotine Tob Res. 2010 May;12(5):530-4.

[6] 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.

[7] McKelvey, K., Ramos, M., Roditis, M., Ramamurthi, D., Halpern-Felsher, B. A Qualitative Analysis of Adolescents' Appeal of Various Tobacco Products. In preparation.

The idea that individuals, and in particular youth, misperceive the relative harms, believing that smokeless tobacco is as harmful as cigarette smoking, is flawed. There are multiple studies showing that youth perceive smokeless to be less harmful than cigarettes and other tobacco products.[8,9] One study showed that adolescents rated various tobacco products as conferring significantly different levels of risks and benefits. Generally, adolescents rated cigarettes as most risky, followed by cigars and chew, with hookah and e-cigarettes rated as least risky.[10]

Other concerns about how adolescents might perceive these SNUS products include:

- Marketing Camel Snus as a product with "less risk" is problematic. There is a well-known tendency for the public to underestimate absolute risk when presented in reference to a higher risk alternative.[11]

- The proposed Camel Snus advertisements, which tout smokeless tobacco as an acceptable alternative to smoking, would conflict and compete with messages not to initiate smokeless tobacco use, such as the FDA Real Cost campaign for rural youth. These competing messages are likely to engender confusion and limit the effectiveness of existing tobacco control efforts.[12]

- The message that Camel Snus contains "less risk" may generate perceptions that extend other alternative tobacco products, including conventional moist snuff and chewing tobacco, leading to increased appeal and uptake of other tobacco products, which would harm public health.

RJR and other Tobacco Companies should NOT be permitted to provide "educational" campaigns

RJR argues that education is needed about the relative risks smokeless tobacco and snus versus smoking and imply that they have developed such educational materials (Executive Summary pages 84-85) and again on page 195: The application notes, "education about relative risks of smokeless tobacco and snus versus smoking has the potential to mitigate the observed misperceptions about relative risk." The MRTP application also suggests that "education" has the potential to "improve U.S. smokers' understanding of combustible nicotine sources compared to smoking."

This idea is problematic because no tobacco industry should be involved in any educational effort, and especially not for youth. Studies of past efforts from tobacco companies to provide tobacco education have found that industry-sponsored curricula are at best ineffective at reducing youth use.[13] Instead, these industry-sponsored curricula provide the public with the sense that the industry is trying to prevent youth use of the product, thus creating a positive image of the industry while also subtly promoting smoking and maintaining a connection with a youth audience.[14,15] Industry-sponsored curricula also downplay the highly addictive nature

[8] Chaffee BW. Cheng J. Cigarette and Smokeless Tobacco Perception Differences of Rural Male Youth. Tobacco Regulatory Science, Volume 4, Number 4, July 2018, pp. 73-90(18)
[9] Wray RJ, Jupka K, Berman S, Zellin S, Vijaykumar S. Young adults' perceptions about established and emerging tobacco products: results from eight focus groups. Nicotine Tob Res. 2012 Feb;14(2):184-90.
[10] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ Across Tobacco Products. Journal of Adolescent Health 58 (2016) 558e566
[11] Rothman AJ, Kiviniemi MT. Treating people with information: an analysis and review of approaches to communicating health risk information. *J Natl Cancer Inst Monogr*. 1999(25):44-51.
[12] Tomar SL, Fox BJ, Severson HH. Is smokeless tobacco use an appropriate public health strategy for reducing societal harm from cigarette smoking? *Int J Environ Res Public Health*. 2009;6(1):10-24.
[13] WHO. Tobacco industry interference with tobacco control. http://www.who.int/tobacco/resources/publications/Tobacco Industry Interference-FINAL.pdf. Accessed August 7, 2018.
[14] WHO. Tobacco industry interference with tobacco control. http://www.who.int/tobacco/resources/publications/Tobacco Industry Interference-FINAL.pdf. Accessed August 7, 2018.

of nicotine and completely disregard how product marketing influences use,[16] and tobacco industries have been shown to promote prevention programs that have been shown to be ineffective at reducing youth tobacco use.[17] Further, exposure to tobacco-sponsored smoking prevention advertising on television is associated with youth having lower perceived risks of smoking and greater likelihood of smoking.[18]

The more relevant question to be answered is how will youth perceive Snus given the marketing claims, including how they perceive Snus compared to other tobacco products, and whether the marketing and appeal of this new tobacco product will result in lower perceptions of risk compared to other tobacco products, which then can result in use.

More specifically, the question is: Will Snus, with lower perceived risks, encourage never-smokers -- including adolescents -- who would otherwise not use any tobacco products to be more likely to try Snus?

In making its determination on whether to issue an MRTP order, FDA is required to take into account "the increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application."[19]

Thus, exposure to the marketing of Snus focusing on claims of reduced risks is likely to cause youth and adolescent never-smokers to initiate nicotine use with Snus. RJR's application is silent on these important issues.

RJR's application failed to consider the likelihood that the Snus flavors would appeal to youth and adolescents and encourage initiation among non-users.

RJR's MRTP application includes the following six varieties of its Camel Snus smokeless tobacco products: Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, and Camel Snus Robust Camel Snus Winterchill.

RJR failed to provide any information on whether these flavored products will attract youth.

In order to attract young and new users, the tobacco industry adds characterizing flavors like mint, menthol, fruit, and candy to tobacco.[20] These flavors appeal to new users by masking the harsh taste of tobacco. Additionally, tobacco products with a characterizing flavor including fruit-flavored e-cigarettes[21] and menthol cigarettes[14] are perceived to be less harmful than unflavored or tobacco-flavored products. In addition, there is some evidence that menthol cigarettes are harder to quit.[22] Snus is no exception in how tobacco flavors and

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[15] CDC Office on Smoking and Health. Tobacco industry-sponsored youth prevention programs in schools. April 2018. https://www.voorheesville.org/site/handlers/filedownload.ashx?moduleinstanceid=538&dataid=1802&FileName=Tobacco%20industry%20sponsored%20youth%20prevention%20programsCDC.pdf. Accessed on August 13, 2018.

[16] Landman A, Ling PM, Glantz SA. Tobacco Industry Youth Smoking Prevention Programs: Protecting the Industry and Hurting Tobacco Control. American Journal of Public Health. 2002;92(6):917-930. doi:10.2105/ajph.92.6.917.

[17] Mandel, LL., Bialous, SA, Glantz, SA. Avoiding "truth:" tobacco industry promotion of life skills training. J Adolescent Health. 2006 Dec;39(6):868-79

[18] Wakefield, M., Terry-McElrath, Y., Emery, S., Saffer, H., Chaloupka, FJ, Szczypka, G., Flay, B., O'Malley, PM, & Johnston, LD. Effect of televised, tobacco company-funded smoking prevention advertising on youth smoking-related beliefs, intentions, and behavior. Am J Public Health, 2006, Dec 96(12): 2154-60.

[19] Section 911(g)(4)(C) of the Family Smoking Prevention and Tobacco Control Act.

[20] Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. N Engl J Med. 2014;370(23):2250-2252.

[21] Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. Tob Control. 2016;25(Suppl 2):ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174.

[22] Pletcher MJ, Hulley BJ, Houston T, Kiefe CI, Benowitz N, Sidney S. Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function. 2006;166.

packaging elements affect youths' harm perceptions: Youth shown packages for smokeless tobacco with or without a flavor descriptor (primarily for snus and dissolvable tobacco) were more likely than older adults to associate the flavor descriptor with better taste, more appeal, and lower health risks.[23]

Flavor or "taste" is one of the most common persuasive marketing techniques used to promote food (mostly candy and snacks) to children on TV.[24] Exposure to ads for flavored products is positively associated with youth consumption,[25] and most money spent by youth is on food or beverages, particularly sweets.[26] Research on e-cigarettes comports with these findings, concluding: flavors play an important role for online e-cigarette marketing and boosts user interaction and positive emotion;[27] flavored (vs. unflavored) e-cigarette ads elicit greater appeal and interest in buying and trying e-cigarettes and the appeal of ads for flavors is linked to rapid and persistent adoption of e-cigarettes among youth;[28] and 75% of US youth stated they would not use e-cigarettes without flavors.[29]

Youth are Attracted to Flavored Tobacco Products

The majority of youth in the US who try tobacco initiate with flavored tobacco products, including 81% of e-cigarette ever users, 65% of cigar ever users, and 50% of cigarette ever smokers.[30] Adolescents are more likely to report interest in trying an e-cigarette from a friend if it is menthol-, candy-, or fruit-flavored than if unflavored.[31] Most adolescent current tobacco users cite flavors as a reason for use (including 81% for past 30-day e-cigarette users; 74% for past 30-day cigar users).[10] Youth and young adult tobacco users are more likely than older adult tobacco users to use flavored products, including menthol cigarettes,[32] flavored smokeless tobacco,[33] and flavored cigars.[34] Young smokers (12-17) are three times as likely to smoke menthol cigarettes as are smokers 35 and older.[35] Adolescents are more likely to report interest in trying an e-cigarette from a

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Trinidad DR, Pérez-Stable EJ, Messer K, White MM, Pierce JP. Menthol cigarettes and smoking cessation among racial/ethnic groups in the United States. Addiction. 2010;105(SUPPL.1):84-94. doi:10.1111/j.1360-0443.2010.03187.x.

[23] Adkison SE, Bansal-Travers M, Smith DM, O'Connor RJ, Hyland AJ. Impact of smokeless tobacco packaging on perceptions and beliefs among youth, young adults, and adults in the U.S: findings from an internet-based cross-sectional survey. Harm Reduct J. 2014 Jan 17;11:2. doi: 10.1186/1477-7517-11-2.

[24] Jenkin G, Madhvani N, Signal L, Bowers S. A systematic review of persuasive marketing techniques to promote food to children on television. Obesity reviews. 2014;15(4):281-293.

[25] Cairns G, Angus K, Hastings G, Caraher M. Systematic reviews of the evidence on the nature, extent and effects of food marketing to children. A retrospective summary. Appetite. 2013;62:209-215.

[26] Kraak VI, Gootman JA, McGinnis JM. *Food marketing to children and youth: Threat or opportunity?* National Academies Press; 2006.

[27] Liang Y, Zheng X, Zeng DD, Zhou X. Impact of flavor on electronic cigarette marketing in social media. 2015:278-283.

[28] Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: An experimental study. *Tob Control*. 2016;25(e2):e107-e112.

[29] Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. *Tob Control*. 2014;23 Suppl 3:iii3-9.

[30] Ambrose B, Day H, Rostron B, et al. Flavored tobacco product use among us youth aged 12-17 years, 2013-2014. *J Am Med Assoc*. 2015;314(17):1-3. doi:10.1001/jama.2015.13802.

[31] Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tob Control*. 2016;25(Suppl 2):ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174.

[32] Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004–2014. *Tob Control*. 2016;25(Suppl 2):ii14-ii20. doi:10.1136/tobaccocontrol-2016-053329.

[33] Oliver AJ, Jensen JA, Vogel RI, Anderson AJ, Hatsukami DK. Flavored and nonflavored smokeless tobacco products: Rate, pattern of use, and effects. *Nicotine Tob Res*. 2013;15(1):88-92. doi:10.1093/ntr/nts093.

[34] Delnevo CD, Giovenco DP, Ambrose BK, Corey CG, Conway KP. Preference for flavoured cigar brands among youth, young adults and adults in the USA. *Tob Control*. 2014;24(4):389-394. doi:10.1136/tobaccocontrol-2013-051408.

[35] Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004–2014. *Tob Control*. 2016:1-7. doi:10.1136/tobaccocontrol-2016-053329.

friend if it is menthol-, candy-, or fruit-flavored than if unflavored,[36] and three quarters of adolescent and young adult flavored tobacco product users reported they would quit if flavors were unavailable.[37]

Flavors in smokeless tobacco enhance perceived product acceptability among youth and likely contribute to youth smokeless tobacco initiation and continued use

Smokeless tobacco products frequently feature the same sweeteners and chemical flavorings found in popular candies.[38] Most adolescent users of smokeless tobacco use flavored smokeless tobacco (69% of ever-users recall first starting with flavored smokeless tobacco; and 81% of current users now use flavored smokeless tobacco).[39] However, among adult (age 25+) smokeless tobacco current users, less than half use a flavored product.[40]

Smokeless tobacco has a strong taste and odor. Potential and new users may need to overcome negative taste and sensation expectations before experimentation. Adding flavors to smokeless tobacco does just that. Adolescent users' preferences for flavored smokeless tobacco may relate to masking the tobacco taste or could correspond to stronger preferences for sweet flavors at younger ages.[41]

Tobacco industry documents show tobacco companies have a long history of adding flavors to smokeless tobacco products to increase youth appeal. The development of flavored smokeless tobacco products as starter products and the initiation steps in a "graduation" process was reported in the scientific literature decades ago.[42] Further analyses of industry documents have shown that tobacco companies (including RJR) have a longstanding deep knowledge of the appeal of flavored smokeless tobacco and "candy brands" to young inexperienced tobacco users, that flavors and sugars both increase palatability and affect nicotine delivery of smokeless products, and mask the harsh and aversive effects of tobacco, facilitating youth initiation and continued use.[43]

Beliefs regarding flavored smokeless tobacco are associated with youth susceptibility to smokeless tobacco use. Using data from the baseline wave of the nationally representative Population Assessment of Tobacco and Health (PATH) Youth Study, Chaffee et al. found US youth age 12-17 who had never tried any tobacco product (N=7,718) were more likely to report that flavored smokeless tobacco was "easier to use" compared to unflavored ST (20.2%) than to report that flavored smokeless tobacco was "harder to use" (5.8%).[44] Individuals

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[36] Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tob Control*. 2016;25(Suppl 2):ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174.

[37] Loukas A, Jackson CD, Marti CN, Perry CL. Flavored tobacco product use among youth and young adults: What if flavors didn't exist? *Tob Regul Sci*. 2017;3(2):168-173.

[38] Miao S, Beach ES, Sommer TJ, Zimmerman JB, Jordt SE. High-Intensity Sweeteners in Alternative Tobacco Products. Nicotine Tob Res. 2016 Nov;18(11):2169-2173. doi: 10.1093/ntr/ntw141.

Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. N Engl J Med. 2014 Jun 5;370(23):2250-2. doi: 10.1056/NEJMc1403015.

[39] Ambrose BK, Day HR, Rostron B, Conway KP, Borek N, Hyland A, Villanti AC. Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014. JAMA. 2015 Nov 3;314(17):1871-3. doi: 10.1001/jama.2015.13802.

[40] Villanti AC, Johnson AL, Ambrose BK, Cummings KM, Stanton CA, Rose SW, Feirman SP, Tworek C, Glasser AM, Pearson JL, Cohn AM, Conway KP, Niaura RS, Bansal-Travers M, Hyland A. Flavored Tobacco Product Use in Youth and Adults: Findings From the First Wave of the PATH Study (2013-2014). Am J Prev Med. 2017 Aug;53(2):139-151. doi: 10.1016/j.amepre.2017.01.026.

[41] De Graaf C, Zandstra EH. Sweetness intensity and pleasantness in children, adolescents, and adults. Physiol Behav. 1999 Oct;67(4):513-20.

[42] Connolly, Gregory N. "The Marketing of Nicotine Addiction by One Oral Snuff Manufacturer." *Tobacco Control* 4, no. 1 (1995): 73-79. http://www.jstor.org/stable/20747349.

[43] Kostygina G, Ling PM. Tobacco industry use of flavourings to promote smokeless tobacco products. Tob Control. 2016 Nov;25(Suppl 2):ii40-ii49. doi: 10.1136/tobaccocontrol-2016-053212.

who reported that flavored smokeless tobacco was easier to use were more likely to be susceptible to smokeless tobacco use than those who reported flavored smokeless tobacco was harder to use, about the same, or that they did not know. Susceptibility was measured using previously validated measures that have been shown to predict tobacco initiation about youth[45] - measures that ask youth to report their curiosity about smokeless tobacco and their willingness and expectations for future use. Adjusted for socio-demographic characteristics and other known tobacco initiation risk factors, such as receptivity to advertising, youth who viewed flavored smokeless tobacco as easier to use were at 1.5-times the odds of being susceptible to smokeless tobacco use than youth with any other perception regarding flavored smokeless tobacco and ease of use.

Couch et al. conducted a qualitative study examining with greater detail how flavors in smokeless tobacco potentially contribute to product appeal and initiation among youth. They interviewed 55 adolescent males at three rural high schools in the Western US, including 32 current or former users of smokeless tobacco. They found that particular flavors, packaging and other product characteristics appeared to enhance curiosity, experimentation, and peer acceptance of smokeless tobacco products.[46] Specifically, participants often associated flavored smokeless tobacco with appealing attributes of non-tobacco products, such as chewing gum, breath mints, food, and alcohol. When discussing smokeless tobacco flavors, one 17-year-old participant said, "It smelled good. So like, I thought, you know, maybe it will taste good, too. I mean, like I said, it was basically the same as gum."[47]

Taken together, these findings show that flavors in smokeless tobacco are viewed favorably among adolescent smokeless tobacco users and potentially play a role in their motivation to initially try smokeless tobacco products and continue to use them. ***RJR ignored this evidence and failed to address how youth will perceive the flavors in the Snus products, that youth will perceive lower risk associated with Snus due to the flavors, and that such flavored Snus products will result in greater likelihood for initiation of Snus among non-users.***

Conclusion

When evaluating whether RJR should be allowed to market Snus as a MRTP, FDA must consider that adolescents who otherwise would not have used any tobacco product might find Snus appealing and will initiate using Snus as their first tobacco product. This is especially likely given adolescents' attraction to flavored tobacco products, the appeal of novel products among adolescents, and the tendency for the public at large, including adolescents, to misinterpret reduced harm claims.

Further, FDA must consider whether the evidence submitted by RJR were *independent studies*, and not studies that were conducted by RJR or influenced or paid by RJR.[48] In particular, FDA must review independent studies of adolescents' perceptions of Snus and the marketing claims made about Snus, as well as independent studies that examine whether in the real world adolescents are more or less likely to initiate with Snus compared to other tobacco products. FDA should review studies that examine adolescent consumers,' potential

[45] Pierce JP, Distefan JM, Kaplan RM, Gilpin EA. The role of curiosity in smoking initiation. Addict Behav. 2005 May;30(4):685-96.
Nodora J, Hartman SJ, Strong DR, Messer K, Vera LE, White MM, Portnoy DB, Choiniere CJ, Vullo GC, Pierce JP. Curiosity predicts smoking experimentation independent of susceptibility in a US national sample. Addict Behav. 2014 Dec;39(12):1695-700. doi: 10.1016/j.addbeh.2014.06.002.
[46] Couch ET, Darius EF, Walsh MM, Chaffee BW. ST product characteristics and relationships with perceptions and behaviors among rural adolescent males: a qualitative study. Health Educ Res. 2017 Dec 1;32(6):537-545. doi: 10.1093/her/cyx067.
[47] Couch ET, Darius EF, Walsh MM, Chaffee BW. ST product characteristics and relationships with perceptions and behaviors among rural adolescent males: a qualitative study. Health Educ Res. 2017 Dec 1;32(6):537-545. doi: 10.1093/her/cyx067.
[48] 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.

consumers,' and non-consumers' perceptions of Snus products, and their use in the real world. FDA must evaluate whether and to what extent adolescents initiate with Snus, whether they are likely to use both Snus and other tobacco products, and whether adolescents initiating with Snus will be more likely to subsequently initiate cigarette use. ***Because RJR did not submit with its MRTP application such rigorous, independent studies and because the application made no consideration of potential impact on adolescents, RJR did not meet its statutory burden under TCA section 911(g) to demonstrate that Camel Snus, as actually used by consumers, will benefit the health of the population as a whole, especially taking into account adolescents and other non-users. Therefore, FDA should deny RJR's MRTP application.***

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

RJR consumer perceptions studies are poorly designed and fail to provide sufficient evidence to evaluate the effects the proposed modified risk advertisements on consumer comprehension and behavioral intentions

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RJ Reynolds Tobacco Company's (RJR) Consumer Reactions studies submitted as part of the RJR's Modified Risk Tobacco Product (MRTP) Applications for Camel Snus are poorly designed so **do not provide sufficient evidence for the FDA to evaluate the effects of the proposed modified risk claims and advertisement materials on consumer comprehension and behavioral intentions**.

- "Consumer Comprehension and Persuasion" studies did not use randomized experimental design, making the assessment of the actual effects of the marketing materials impossible.
- "Likelihood of Use" studies selectively asked different behavioral intentions questions of smokers with and without quitting intentions, preventing the comparison between the groups and evaluation of the effects of modified risk claims on dual use behavioral intentions among smokers with quitting intentions.

Throughout the application materials made public by the FDA, the applicants make unsubstantiated claims (e.g., their advertisements "further educate smokers about the risks of cigarette smoking"), base their claims on incomplete literature review, and misrepresent their own findings. Because of these shortcomings, the MRTP applications do not provide sufficient evidence that introduction of these modified risk claims would have population level benefits and, therefore, should be denied.

Background

On December 18, 2017, FDA filed for substantive scientific review six RJ Reynolds Tobacco Company's (RJR) Modified Risk Tobacco Product (MRTP) Applications for the following six varieties of its Camel Snus smokeless tobacco products: Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust Camel Snus Winterchill. RJR proposed three different modified risk advertising executions for each of the six Camel Snus styles, and thus requested a total of 18 MRTP orders.

RJR's three proposed MRTP advertising executions are:

- **Modified risk execution #1**

Smokers who **switch completely** from cigarettes to Camel SNUS can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.

- **Modified risk execution #2**

Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS greatly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.

- **Modified risk execution #3**

Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer and respiratory disease.

RJR's proposed advertising plan includes print advertising, direct mail, e-mail, a branded website (snusnation.com), and direct consumer engagement.

To evaluate consumer reactions to these modified risk claims, RJR conducted six studies: three "Comprehension & Persuasion" studies and three "Likelihood of Use" studies (Table 1).

Table 1. Consumer reactions studies that RJR submitted as part of the MRTP applications.

Study Name	Study Design	Study Timeline	Study Participants
Execution 1 Comprehension & Persuasion Study	Online survey (non-randomized)	October 20 - October 30, 2014	8,404 adults drawn from a national web panel
Execution 2 Comprehension & Persuasion Study	Online survey (non-randomized)	June 24, 2015 - July 21, 2015	4,924 adults drawn from a national web panel
Execution 3 Comprehension & Persuasion Study	Online survey (non-randomized)	June 16 - July 21, 2015	4,906 adults drawn from a national web panel
Execution 1 Likelihood of Use Study	Online randomized experiment	November 24 - December 22, 2014	14,511 adults drawn from a national web panel
Execution 2 Likelihood of Use Study	Online randomized experiment	August 11 - September 30, 2015	11,302 adults drawn from a national web panel
Execution 3 Likelihood of Use Study	Online randomized experiment	August 11 - September 30, 2015	11,305 adults drawn from a national web panel

1. RJR's "Consumer Comprehension and Persuasion" studies do not demonstrate how the advertisement materials affected understanding and consumer comprehension because they did not use randomized experimental design.

The Family Smoking Prevention and Tobacco Control Act (FSPTCA)[1] requires that for FDA to issue an order allowing for a tobacco product to be marketed as a modified risk tobacco product, it must establish "that any advertising or labeling concerning modified risk products 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." The use of causal language in the FSPTCA ("enable") means that the evidence submitted in support of this requirement should establish that advertisement or labeling under consideration have an effect on

[1] Family Smoking Prevention and Tobacco Control Act§ 911(h)(1), 21 U.S.C. § 387k{h}{1}. Retrieved from http://www.gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf .

or cause the consumers to understand the modified risk information. In the application, RJR similarly states that the goal of the "Comprehension and Perceptions" studies was "to assess the effects of the proposed modified risk advertising for Camel Snus on current tobacco users' and non-users' (both former users and never users) understanding and application of the modified risk information" (p. 196, Executive Summary).

To address the effect of marketing on consumer understanding and perception, FDA recommends in its Guidance on MRTP applications[2] that applicants submit human studies regarding consumer understanding of the product, including its labeling, marketing and advertising. The scientific studies submitted by the applicant should inform FDA's evaluation of the product's marketing on consumer perception and understanding, including:

- The ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health;
- Consumers' beliefs about the health risks of using the product relative to other tobacco products, including those within the same class of products;
- Consumer beliefs about the health risks of using the product relative to cessation aids; and
- Consumer beliefs about the risks of using the product relative to quitting all tobacco use.

However, "Comprehension and Perceptions among Tobacco Users and Non-Users" studies submitted by RJR as part of the MRTP application cannot be used to support the causal claim because they did not use an experimental design that allows for the establishment of causality.

The RJR makes at least four causal claims about the results of its studies:

- "RJRT's studies show that the proposed advertising will be successful in communicating reduced risk information to consumers while avoiding overgeneralization of the risk messaging, which in turn would be expected to mitigate any potential for the advertising to deter tobacco quitting or promote tobacco initiation." (p. 193, Executive Summary).
- "Respondents did not develop a misperception that it had no risk at all. […] In sum, the proposed advertisements communicated conservative risk reduction messaging, and did not promote misconceptions that might lead to inappropriate use of Camel Snus or lead to unintended effects that would reduce the population benefit of having smokers switch completely to Camel Snus." (p. 203, Executive Summary).
- "Taken together, these findings support the conclusion that, overall, consumers understand - and are not mislead by - the proposed Camel SNUS modified risk messaging materials." (p. 24, in Amended Final Report – Execution 1 Comprehension & Persuasion Study, p. 24 in Amended Final Report – Execution 2 Comprehension & Persuasion Study, p. 24 in Amended Final Report – Execution 3 Comprehension & Persuasion Study).
- "The research measured the effects of a single exposure to the proposed Camel SNUS modified risk messaging materials" (p. 26, Amended Final Report – Execution 1 Comprehension & Persuasion Study, p. 26, Amended Final Report – Execution 2 Comprehension & Persuasion Study, p. 26, Amended Final Report – Execution 3 Comprehension & Persuasion Study).

[2] FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance (March 2012).

These causal claims cannot be made because the "Comprehension and Perceptions" studies did not use a randomized experimental design. These studies did not randomize participants to groups in which one group saw the proposed messages while another (control) group saw content not related to modified tobacco risks. Instead, in these studies the administrators simply showed the same advertising materials to all participants and then asked them about their beliefs. Because they did not use an appropriate experimental design, it is impossible to evaluate if it was the ads that caused these perceptions or if people already had them. It might be that ads actually made people LESS LIKELY to correctly understand the information, but without a control group it is impossible to exclude these possibilities.

2. Contrary to the RJR's claims, the proposed Camel Snus modified risk advertising materials do not "further educate smokers about the risks of cigarette smoking."

In the Executive Summary, RJR claims: "RJRT has designed the proposed Camel Snus modified risk advertising materials to further educate smokers about the risks of cigarette smoking, in more detail than the statutory warning labels" (p. 84) On the next page, they further state, "RJRT believes that the worst case scenario should FDA issue MRTP orders for Camel Snus is that smokers will not switch to Camel Snus in significant numbers, but will have increased opportunities to learn more about the risks of continuing to smoke."

What content on the proposed advertisements "educates smokers about the risks of cigarette smoking?" The RJR refers to the "balancing information" that contains the following: "The proposed print advertising also provides health-related balancing information stressing the importance of quitting and not starting tobacco use: 'Like all tobacco products, Camel SNUS contains nicotine and is addictive. Adults who do not use or have quit using tobacco products should not start. Minors and pregnant women should never use tobacco products. If you're a smoker concerned about the health risks from smoking, the best choice is to quit. If you're a smoker concerned about the health risks from smoking, the best choice is to quit. A good place to begin is talking with a healthcare provider.'"

RJR claims the comparative risk information (such as "reduced risks", "no smoke = less risk", "less risk", "fewer carcinogens", "less of the harmful chemicals than cigarette smoke", "smoke-free, so there are no secondhand smoke risks for those around you", and the full modified risk claim) also indirectly communicates the risks of smoking.

However, these statements do little to educate smokers about the devastating effects of smoking. Extensive research has shown that to effectively communicate harms of smoking and make people really understand the risks,[3] messages need to be graphic, emotional, and hard-hitting.[4]

[3] Slovic P, Finucane ML, Peters E, MacGregor DG. Risk as analysis and risk as feelings: Some thoughts about affect, reason, risk, and rationality. *Risk Analysis.* 2004;24(2):311-322. Weinstein ND. What does it mean to understand a risk? Evaluating risk comprehension. JNCI Monographs. 1999;1999(25):15-20.

[4] Noar SM, Hall MG, Francis DB, Ribisl KM, Pepper JK, Brewer NT. Pictorial cigarette pack warnings: a meta-analysis of experimental studies. *Tobacco Control.* 2016;25:341-354. Noar SM, Francis DB, Bridges C, Sontag J, Ribisl KM, Brewer NT. The impact of strengthening cigarette pack warnings: Systematic review of longitudinal observational studies. Social Science & Medicine. 2016;164:118-129. Hammond D. Health warning messages on tobacco products: a review. Tobacco Control. 2011;20:327-337. Wong NC, Cappella JN. Antismoking threat and efficacy appeals: effects on smoking cessation intentions for smokers with low and high readiness to quit. *J Appl Commun*

The informational bits in the proposed Camel SNUS advertisements do very little to increase the smokers' perceived risks of smoking.

In the "Comprehension and perceptions" studies, participants' perceived risks of smoking were measured. However, because these studies did not employ randomized experimental design with a control group, it is impossible to tell if the ads had any effect on the perceived risks of smoking. Indeed, they likely did not; in our recently published study,[5] we found that comparative risk messages about e-cigarettes, even when they emphasized harmful effects of smoking, did not increase perceived risks of smoking among smokers, probably because they were already high.

Thus, the RJR's claim that the modified risk marketing materials "further educate smokers about the risks of cigarettes smoking" is unsubstantiated and cannot be used as a justification for allowing these claims.

3. RJR presents an incomplete literature to support their claim that consumers overestimate risks of smokeless tobacco compared to cigarettes.

Similar to their arguments and literature review in RJR's 2011 Citizen Petition requesting that FDA change one of the smokeless tobacco warning labels from "WARNING: This product is not a safe alternative to cigarettes" to "WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes",[6] RJR claims that "the overwhelming majority of U.S. adults incorrectly believe smokeless tobacco and snus to be either just as harmful or more harmful than traditional cigarettes" (p. 194, Executive Summary). In contrast, based on a nationally representative sample of adult smokers,[7] we found that "whether people perceive smokeless tobacco products (including snus) as less harmful than cigarettes depends on how the question is framed." Specifically, in our survey of a nationally representative sample of 1,836 smokers, we found that when we asked a single question about comparative risk (e.g., "Compared to smoking cigarettes, using new smokeless tobacco, such as snus, is… less harmful/equally as harmful/more harmful"), only 22.1% of respondents reported snus as less harmful. However, when we asked two separate questions (e.g., "In your opinion, how harmful are new smokeless tobacco products, such as snus, to general health?" and "In your opinion, how harmful is smoking cigarettes for health" with answers on 1-7 scales), and then compared the answers to the two questions, we found that 51.6% of participants reported snus as less harmful (Figure 1).

Res 2009;37:1–20. Farrelly MC, Duke JC, Davis KC, et al. Promotion of smoking cessation with emotional and/or graphic antismoking advertising. American journal of preventive medicine. 2012;43(5):475-482.

[5] Yang B, Owusu D, Popova L. Testing messages about comparative risk of electronic cigarettes and combusted cigarettes *Tobacco Control* Published Online First: 13 August 2018. doi: 10.1136/tobaccocontrol-2018-054404

[6] Reynolds R.J. Citizen petition. 2011 Available at: http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0573-0001. Accessed August 20, 2018.

[7] Popova L, Ling PM. Perceptions of Relative Risk of Snus and Cigarettes Among US Smokers. *American Journal of Public Health.* 2013;103(11):e21-e23.

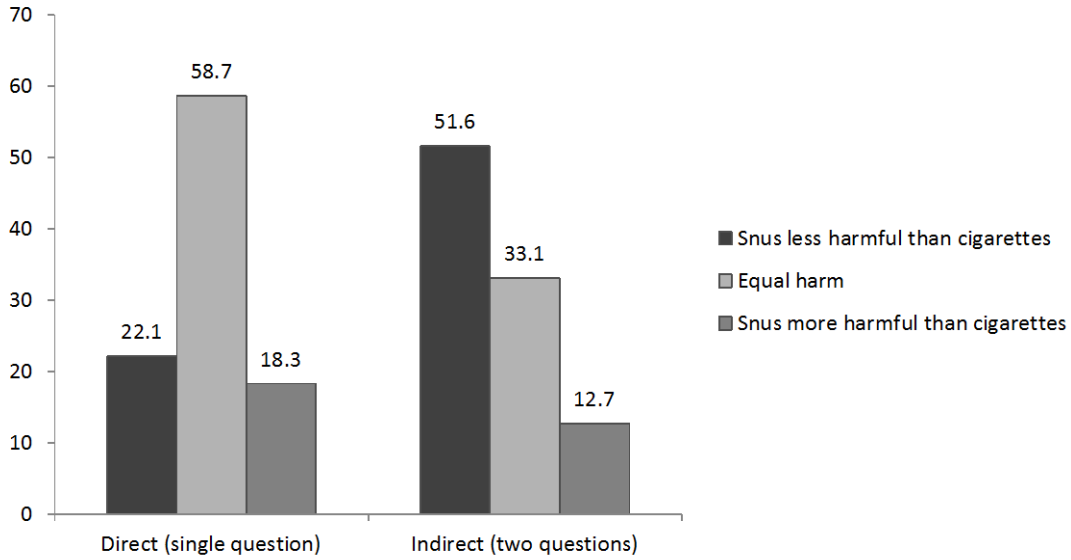

Figure 1. Percentage distribution of US adult current and recently former smokers by relative degree of perceived harm from using snus or smoking cigarettes: November 2011. (Source: Popova L, Ling PM. Perceptions of Relative Risk of Snus and Cigarettes Among US Smokers. *American Journal of Public Health.* 2013;103(11):e21-e23.)

These data show that the proportion of people believing that smokeless tobacco is less harmful than are cigarettes may be substantially larger than RJ Reynolds claims because most of the studies cited in the RJ Reynolds petition measured comparative risk perceptions with a single question. In its Camel SNUS MRTP application, RJR once again uses primarily studies that used a single question to assess comparative risk perceptions. Therefore, their claim that consumers misperceive the relative harm of snus and cigarettes is not supported to the extent that they claim.

4. RJR's executive summary misrepresents the RJR's own findings: The executive summary claims that advertisements did not increase interest among smokers who are likely to quit, but the reports for actual studies demonstrate that advertisements increased interest in both smokers who are and are not likely to quit.

In summarizing the results of the "Likelihood of Use" studies, RJR's Executive Summary claims that for "smokers likely to quit", "their interest was not increased among those who viewed the modified risk advertising" (p. 212, Executive Summary). However, in "Execution 1 – Likelihood of Use Study", "among self-defined current regular cigarette smokers by potential quitter status (refer to Table A-7 in Appendix A for distributions of intent ratings) a two-factor ANOVA reveals significant main effects of potential quitter status ($p<.0001$) and arm ($p<.05$), but no interaction between those two factors ($p>.05$)" (p. 27, Execution 1 – Likelihood of Use Study. The results were the same for current regular cigarette smokers, p. 27 in Execution 2 – Likelihood of Use Study and p. 27 in Execution 3 – Likelihood of Use Study). Thus, RJR's own data show that ratings of likelihood to purchase Camel SNUS for personal trial among potential cigarette quitters are significantly lower than among consumers who are not likely to quit cigarettes in both the test and control arms, and ratings are higher in the test arm than in the control arm" (p. 28, Execution 1 – Likelihood of Use Study). (Similar findings are reported on p. 22 and p. 28 Execution 2 – Likelihood of Use Study and on p. 22, 26, and 26 Execution 3 –

Likelihood of Use Study). ***Thus, RJR's own results indicate the proposed modified risk advertising increases interest in trying snus among both smokers who do and do not plan to quit smoking (Figure 2).***

Table 9B: Weighted Mean Likelihood to Purchase for Personal Trial Ratings - Test versus Control Camel SNUS Advertising Materials among Current Regular Tobacco Users by Potential Quitter Status† -

	Current Regular Tobacco Users	Potential Tobacco Quitters	Not Potential Tobacco Quitters
Test (with modified risk messaging)	**3.7^ (.19)** (n*=1,735)	**2.6 (.39)** (n*=253)	**3.8 (.20)** (n*=1,482)
Control (without modified risk messaging)	**3.3 (.18)** (n*=1,733)	**2.2 (.33)** (n*=226)	**3.5 (.19)** (n*=1,507)

† Tobacco status is based on self-reported tobacco usage.

* Unweighted sample size (on which the weighted data are based).

^ Statistically significantly higher than control (denotes significance from previous analysis; *refer to Table 9A*).

Numbers in parentheses represent the 95% confidence interval half-width (± mean estimate).

Figure 2. Mean likelihood of purchase is significantly higher among current regular tobacco users exposed to the modified risk advertisements regardless of whether they are potential quitters or not[8]. (Source: p. 22, Execution 3 – Likelihood of use study).

Increased interest in snus among smokers with quitting intentions represents a population level harm because in the absence of product promoted as lower risk they would try to quit smoking. RJR tries to gloss over these findings by arguing that potential quitters interested in trying snus are not going to diverge from their quitting trajectory because about half of them state they "envisioned" using snus to help them quit. In addition, RJR states that "(20-36%) just wanted to try it out of curiosity, also suggesting it would be unlikely to deter quitting." It is unclear how trying it out of curiosity has no negative effects of quitting. Most kids start using tobacco products "out of curiosity" and then continue to become lifetime smokers. Importantly, there are a lot more smokers with quitting intentions than without (our recent study found that 86% of smokers plan to quit while only 14% never plan to quit)[9], which indicates that increased interest in snus among potential quitters would have a population-level harm.

[8] On p. 22, Execution 3 – Likelihood of use studies, the report states: "A two-factor ANOVA reveals significant main effects of potential quitter status ($p<.0001$) and arm ($p<.05$), but no interaction between those two factors ($p>.05$). Thus, ratings of likelihood to purchase Camel SNUS for personal trial among potential tobacco quitters are significantly lower than among consumers who are not likely to quit tobacco in both the test and control arms; and, ratings are higher in the test arm than the control arm." The findings are the same for Execution 2 (p. 22, Execution 2 – Likelihood of use studies). For Execution 1, there was no significant main effect of arm (p. 22, Execution 2 – Likelihood of use studies).

[9] Popova L, Majeed B, Owusu D, Spears CA, Ashley DL. Who are the smokers who never plan to quit and what do they think about the risks of using tobacco products? *Addictive behaviors.* 2018;87:62-68.

5. "Likelihood of use" studies selectively asked some questions of smokers with and without quitting intentions in a way that obfuscates the effects of these advertisements on different groups.

In determining whether the modified risk order would have a population level benefit, it is important to evaluate the potential extent of dual use – use of snus in addition to smoking or other tobacco product use. RJR's "Likelihood of use" studies aim to measure self-reported dual use intentions. They ask the question, but only of smokers who are "current regular users" of tobacco who are not intending to quit (if they showed some interest in trying Camel snus, specifically, if they rated likelihood to purchase as "2" or greater). These smokers were asked:

"You indicated you have some interest in purchasing Camel SNUS in order to try it. How would you envision using Camel SNUS?

- Instead of current tobacco (stop using current tobacco completely)
- In addition to current tobacco (overall increase in tobacco use)
- In place of some of current tobacco (no net increase in tobacco use)
- Don't know"

Current regular tobacco users who have intentions to quit (i.e., "potential quitters") were not asked this question. Instead, they were asked the reasons for being interested in trying snus:

"You indicated that you plan to quit using tobacco, but that you have at least some interest in purchasing Camel SNUS in order to try it (that is, you did not rate your intention to try Camel SNUS a "1" in the previous question). Which one of the following reasons best explains why you have some interest in trying Camel SNUS? (Select one.)

- To help me quit
- It will allow me to use tobacco in situations where I cannot use my current product
- I'm just curious about it
- Don't know"

The studies should have measured dual use intentions among all smokers, regardless of the quitting intentions. All smokers should have been asked both questions. It would have allowed to demonstrate the level of dual use intentions among smokers with and without quitting intentions. Currently, the second question (the one that was asked of potential quitters only) is used by RJR to argue that even though interest in snus increased in potential quitters after seeing the modified risk advertisements, because about half of them selected "to help me quit" as the reason, modified risk advertisements will not suppress their quitting. However, without asking how they envision using snus, it is not possible to claim that they will not engage in dual use in large numbers.

6. Additional comments.

It is impossible to evaluate how these advertising materials were developed since this information on the application is redacted (e.g., all content on pp. 5-53 of the "Section 4 – Labels, Labeling, and Advertising" is not available. It should be made available for comment and evaluation by the public.)

Further, it appears that RJR collected but did not present data related to health literacy in their research, which may be relevant to the impact of the advertising on vulnerable populations; this data should be made available for comment and evaluation by the public.

RJR tries to downplay the evidence that snus serves as a gateway to cigarette smoking. In discussing the role of smokeless tobacco as a gateway to smoking, the application cites some studies that found the evidence of this gateway. They explain this finding by claiming that smoking is prohibited during basic military training, but smokeless tobacco is not:

> "A study of U.S. Air Force recruits found an increased odds of smoking initiation (OR=2.33; 1.84-2.94) among current smokeless tobacco users compared to non-users, and also among former smokeless tobacco users compared to never users (OR=2.27; 1.64-3.15) (Haddock et al. 2001). It is possible that there are differences between the national samples and the military cohort that account for the different conclusions. Particularly important may be the prohibition of any smoking during military training, which might have resulted in use of smokeless tobacco as a default product until cigarette use was again permitted, leading to what can be viewed as gateway but might actually be an artifact of the controlled environment" (RJR, p. 209, Executive Summary).

However, all tobacco products, including smokeless tobacco, are prohibited during basic military training.[10] Thus, ***RJR is either ill-informed or deliberately distorting the truth. Both of these options raise doubt about the validity of other claims in the application.***

FDA should make all application materials public and the **Camel Snus MRTP Applications should not be approved without sufficient opportunity to examine their contents in their entirety.**

Summary

RJR consumer perceptions studies are poorly designed and do not provide sufficient evidence to evaluate the effects the proposed modified risk advertisements on consumer understanding of claims and behavioral intentions, particularly regarding dual use intentions among potential quitters. These MRTP applications should be denied.

[10] Department of Defense Instruction 1010.15: Smoke-Free Workplace. Washington, DC, Department of Defense, 2001. Available at http://www.dtic.mil/whs/directives/corres/pdf/i101015_010201/i101015p.pdf; accessed March 13, 2007.

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The *Dynamic Population Modeler (+1)* Used to Show Population Health Benefits Does Not Justify Issuing a MRTP Order for Camel SNUS Products

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Background

R.J. Reynolds (RJR) is seeking a Modified Risk Tobacco Product (MRTP) order for six Camel SNUS smokeless tobacco products. In order to be granted this order, the FDA must determine that: (1) the product, as actually used, will reduce harm and risk of tobacco related disease to users, and (2) marketing the products as MRTP will have benefits for the health of the population as a whole, including users and non-users of tobacco products.

It is important to recognize that RJR's burden to demonstrate that marketing Camel Snus will benefit for the health of the population as a whole is as essential as the requirement to show that Camel Snus use will significantly reduce harm or the risk of tobacco-related disease. In making its determination, FDA must consider, among other things, the risks and benefits to all persons who may potentially use or be exposed to Camel Snus, and must compare the health risks of Camel Snus to other consumer behaviors, including:

- The health risks associated with use of Camel Snus as compared to using other tobacco products on the market (including other smokeless tobacco or snus products such as Swedish Match snus);
- Changes in health risks to users who switch from using another tobacco product (including e-cigarettes and other kinds of smokeless tobacco such as Swedish snus) to Camel Snus;
- Health risks associated with switching to Camel Snus as compared to quitting the use of tobacco products altogether;
- The health risks associated with using Camel Snus in conjunction with other tobacco products (i.e., "dual use" or "poly use");
- The health risks associated with switching to Camel Snus as compared to using an FDA-approved tobacco cessation medication;
- The health risks associated with initiating use of Camel Snus as compared to never using tobacco products, including potential gateway effects; and
- Risks to non-users, including risks associated with spitting and environmental waste.[1](page 18-19).

In addressing the effect of an MRTP on the population as a whole, FDA recommends that applicants submit quantitative estimates of the effect the proposed marketing may have on population health. These estimates should integrate all the information regarding the marketing of the product and its potential effects on health, tobacco use behavior and tobacco use initiation to assess the effect that product would have on overall tobacco-related morbidity and mortality.[1](pp.

21-22) FDA recommends that applicants quantify the potential changes in morbidity and mortality to the various types of affected individuals in the U.S. population, including:

- Tobacco users who switch from other commercially marketed tobacco products to the proposed product;
- Tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk;
- Tobacco users who opt to use the proposed product rather than cease tobacco use altogether;
- Tobacco users who opt to use the proposed product rather than an FDA-approved tobacco cessation medication;
- Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users;
- Tobacco users who use the product in conjunction with other tobacco products; and
- Non-users who experience health risks from the product.[1] (p. 22)

In its Guidance, FDA acknowledges the difficulties inherent in making premarket assessments of the effect of marketing a MRTP would have on the population as a whole and the public health, and therefore encourages using statistical models to forecast the population effect and demonstrate an impact on population health.[1](p. 27) For this purpose, RJR uses its Dynamic Population Modeler (DPM) (+1). The model incorporates a number of assumptions, some based on empirical observation and others based on expert opinion or hypothetical use studies with adults. These assumptions determine whether SNUS marketed under a MRTP order will benefit population health or not.

The DPM is described in section 2.13 *Statistical Modeling of the Effects on the Health of the Population as a Whole* of the Executive Summary. We reviewed this model both in terms of the reasonableness of the assumptions as well as whether it satisfies FDA requirements for MRTP orders.

Assessment of the DPM (+1)

- **RJR describes the model as a "fit-for-purpose statistical modeler"** (section 2.13.1, page 221).
    - It follows a cohort of males with no tobacco use at age 13 through age 72.
    - The model compares a base-case in which only cigarettes are smoked to a counterfactual case that includes use of Camel SNUS marketed as an MRTP.
    - The sole outcome considered is survival (mortality).
    - The net benefit to the population is primarily through the effect of snus use on smoking cessation among current cigarette smokers who would otherwise not have quit smoking.

- **The model only considers mortality, despite the fact that tobacco use (including snus) causes considerable morbidity**
    - Models are based on males, but projections are adjusted for male vs female differences taking into account lower survival benefits for females (19% less than males), different smoking rates, and actual population numbers for males and females for 2005 (Executive Summary, 2.13.3, pp. 234-235).

- RJR asserts that "tipping points" would be similar but does not provide specific evidence to support this assumption
- Scenarios consider mortality from lung cancer, oral cancer, respiratory disease, and heart disease. No other cancers are considered, and the diseases included in the respiratory and heart disease categories are not clearly defined.
- The model defines population health as "survival" (p. 233, 2.13.3). No measures of morbidity are included.
- The cohort is modeled from age 13-72. Stopping at 72 misses most mortality, which occurs after that. It may be that "premature mortality" is defined as occurring before 72 but this is not clearly stated.
- By excluding morbidity and mortality after age 72, the model likely underestimates the adverse population effects of approving the MRTP application.

- **Dual/poly users are assumed to have the same risk as 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,[2] 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 impact on population health is likely underestimated

- **The model was validated but the data used for validation are problematic**
  - The base case for the US was validated using 1980 smoking initiation (Substance Abuse and Mental Health Services Administration 1999, full citation not provided) and cessation rates (RJR cites Messer et al. 2007, but does not provide the full citation). They found the rates to be within .2% of the actual age-specific survival probabilities estimated using the 2006 U.S. life table (Arias 2010, full citation not provided) (page 223).
    - More recent life tables for the US are available.[3] Newer life tables would reflect lower mortality rates due to reduced smoking prevalence and other lifestyle interventions.
  - The counterfactual case was validated using Swedish male data on the use of snus (Lundqvist et al. 2009, full citation not provided). The predicted estimates of mortality were within 0.3% of the actual age-specific survival probabilities estimated using the 2006 Swedish life table. However, Swedish data may differ from the US because:
    - Swedish input parameters are very likely different from US input parameters
    - Swedish SNUS have lower nitrosamine levels than the SNUS sold in the US and would thus be likely to result in lower mortality rates.
  - By overestimating mortality in the base case and underestimating mortality in the counterfactual case, the model is biased towards a higher reduction in mortality compared to the counterfactual case.

- **The model does not use the most recent data on smoking initiation/cessation**.
    - On Page 243 of the Executive Summary, RJR indicated that both their multiple cohort full population analysis model and the single-cohort analysis model used the 2000 mortality rates, the 2009 smoking initiation rates, and 2005-2008 smoking cessation rates. However, they did not provide the data sources for these parameters. There are newer available data for all these measures.
    - Given the substantial declining trend in cigarette smoking in recent years, these data are likely to overestimate cigarette initiation and underestimate cessation, leading to an overly positive impact of SNUS compared to cigarettes.

- **Tobacco use transitions are based on RJR research with "large groups of adults" to ask likelihood of use**
    - This is described in Section 6.3 of the application which as of August 15, 2018 was not publicly available, precluding evaluation of the valididity of the values that RJR uses in its model.
    - These findings were converted into estimated probabilities of use using a previously developed algorithm (Section 2.13.2.1). The reference for this algorithm is not provided so there is no way to assess its validity.
    - Transitions among different tobacco use categories are critical parameters in the DPM (+1), but the rates used cannot be fully assessed due to lack of information.

- **The model assumes that switching rates (from cigarette to SNUS use) are much greater than additional initiation rates (from never tobacco users to SNUS use) under MRTP marketing (page 232)**

    - The assumed probability of "switching to snus use" among current cigarette smokers who otherwise would have continued smoking was:
        - 14.2%-16.5% for smokers aged 18-62
        - 1.7%-3.1% for smokers aged 63-72
        - Assumed no switching would occur before age 18
        - These switching rates are higher than those reported elsewhere. One randomized controlled trial found that while 82% of smokers offered free SNUS tried the product, only 4% were using SNUS after 12 months.[4] This study also found that SNUS users were less likely to attempt to quit smoking and did not smoke fewer cigarettes per day.
    - The probability of "additional initiation" of snus use among never tobacco users is merely 0.3%
    - Thus, the "switching" probability is 47-fold or 55-fold higher than the "additional initiation" probability.
    - It is the high switching rate compared to the low initiation rates that is primarily responsible for the net positive impact on population health (page 235).
    - These assumptions bias the model toward finding a positive impact of approving the MRTP application on population health.

- **Diversion from quitting is considered in the model to decline with age**
    - The model assumes an increase in population harm resulting from the "diversion from quitting" of cigarette smokers who would have quit but instead switch to Camel

SNUS. This effect declines with age. Rates are based on the likelihood of use studies for those who had engaged in quitting behaviors and expressed interest in SNUS (Executive Summary, 2.13.2.1.2.2, page 233). Rates of those who would have quit but instead use SNUS are:
    - 8.6 – 20.0% for smokers aged 18-22
    - 1.6-2.2% for smokers aged 68-72
  - The model that is scaled for a mixed gender cohort shows that diversion from quitting results in an additional 900-1700 deaths, and 4,400 – 7,300 if some of those who switch to SNUS instead of quitting relapse to cigarette smoking (Executive Summary, Table 2.13.3-2, page 238).
  - Because these estimates are based on likelihood of use studies rather than empirical data, it is difficult to judge their veracity.

- **Gateway effects are considered but assumed to be small**
  - The models assume that half of the snus initiators would become cigarette smokers (i.e., gateway effect), but this estimate is based on a very low probability of never tobacco users transitioning to initiate snus use - .3% in each age interval (see Figure 2.13.2-1, page 229 and Section 2.13.2.1.2.1, page 231)
  - There is limited data on SNUS initiators who do not use other tobacco products
    - A 2012 telephone survey of 3,627 US adults found that .1% used SNUS alone[5]
    - A recent analysis of the Population Assessment of Tobacco and Health (PATH) data found that 1.0% of youth had ever used smokeless tobacco only (including SNUS) in 2013-14. These youth were 1.5 to 4.3 times as likely to be using cigarettes a year later depending on what covariates were controlled in the model,[6] a much larger effect that RJR assumes.
  - The low rate of SNUS initiators is consistent with available evidence, but the rate of transitioning to cigarette smoking is low compared to empirical evidence, so the negative impact of the gateway effect is probably underestimated in the model.

- **The Excess Relative Risk (ERR) of smoking vs SNUS assumption is critical**
  - The model assumes SNUS is 11% as risky as smoking for 35-49 year olds and 8.2% as risky for those aged 50 and older, based on comparing long-term SNUS users and long-term cigarette smokers. This excess relative risk estimate is based on the opinions of a nine-person panel of experts who were asked to estimate mortality risks associated with long-term use of low-nitrosamine smokeless tobacco after reviewing the available published scientific literature as of 2003.[7]
    - A Delphi approach was used via e-mail to obtain estimates for the 2 age groups for lung cancer, heart disease, and oral cancer. Three rounds were conducted to reach a convergence. Estimates differed substantially by disease category, but an adjusted mean value was used for total mortality.
    - Using an adjusted mean value across disease categories increases the excess relative risk used for lung cancer and reduces the excess relative risk used for oral cancer. For heart disease, the category likely to be responsible for the largest number of deaths, the RJR model uses the mean values of 11.0% and 8.2% for the 2 age groups compared to the values the experts estimated of 10.8% and 11.1%. Using a lower excess relative risk for older tobacco users

may introduce a substantial bias in mortality estimates toward underestimating the effects.

- The low-nitrosamine product considered reflects Swedish SNUS. However, US SNUS uses tobacco with higher nitrosamine levels, so this is not an accurate comparison.
- This key model parameter is not based on any observed data
- Section 6.4 apparently does sensitivity analyses, but this section was not available to review as of August 15, 2018.
- Tipping point analysis (essentially a breakeven analysis) looks at what percent of smokers would have to switch to SNUS to offset adverse effects. Based on the assumption of SNUS being .08-.11 times as harmful, only 2% would need to switch for a net benefit.
- Sensitivity analyses re the tipping point for excess relative risk found that as long as the ERR was less than 46-48% that of cigarettes, the effect on population health is net positive (Page 242, Section 2.13.3.3.1).
  - This statement is true only if all the other assumptions for the main model remain unchanged, including the very low "additional initiation" probability of 0.3%. If the "additional initiation" probability is indeed 30-fold or 40-fold higher, the results of break-even relative risk would be much lower than 46%-48%.
  - The analysis does not compare the effects of SNUS with e-cigarettes or other forms of smokeless tobacco
- The estimates of the excess relative risk are quite low and not based on empirical evidence.
- If the estimates of excess relative risk were more realistic or if the excess relative risk of SNUS were compared with a lower risk tobacco product such as e-cigarettes, there would be a more negative impact on population health.

- **RJR acknowledges that they omit the possibility that SNUS use may delay smoking cessation**
  - The impact of including this in the model would be to reduce the benefit of marketing SNUS as an MRTP by increasing smoking-attributable mortality.

- **Contrary to FDA guidance, RJR ignores morbidity**
  - FDA guidelines state that scientific studies submitted by the applicant "should contain an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality (page 21).[1]
  - RJR does not include any measures of morbidity, including tobacco-caused disease incidence or tobacco-attributable healthcare costs. For cigarettes, morbidity is much greater than mortality: in the US, 6.9 million adults reported smoking-related diseases in 2009[8] while smoking causes 500,000 deaths a year.[9]
  - Wang et al.[10] 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 model does not consider people who may switch from e-cigarettes to SNUS**
  - No attempt is made to model potential initiation among users of other tobacco products, such as e-cigarettes.
  - The model only considers people who initiate with cigarettes or SNUS, but many young people initiate with e-cigarettes.
  - Because e-cigarettes are likely to have a lower mortality risk than cigarettes, the excess relative risk of SNUS vs. e-cigarettes may be positive or negative, and switching from e-cigarettes to SNUS 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**
  - Potential health risks from SNUS to non-users, such as infections from exposure to expectorate or environmental waste are not considered.
  - Insofar as SNUS impacts cigarette smoking, such as a gateway effect leading to smoking or reducing smoking cessation, the model needs to consider the impact of secondhand smoke on non-smokers.
  - Omitting the impact of SNUS use on non-tobacco users will lead to an underestimation of the harm to the population of marketing SNUS as an MRTP.

- **Sensitivity analyses are designed to favor a positive impact on population health of a SNUS MRTP order**
  - The base of the assumed "additional initiation" probability is very low (i.e., at 0.3%). Thus reducing it by 75%in the sensitivity analyses leads to almost zero initiation probability (i.e., 0.075%).
  - For the "switching" probability, the 75% reduction of 14.2%-16.5% leads to a new level of 3.55%-4.15%, which is still about 47-fold or 55-fold higher than the "additional initiation" transition probability.
  - A more realistic assumption for sensitivity analyses would be to increase the "additional initiation" probability by at least 20-fold or 30-fold to the level of 6.0% or 9%. In this way, the results shown in Table 2.13.3-1 for the population-level harmful effect under "additional initiation" and "additional initiation with Gateway Effect" would be much larger in terms of absolute magnitude.
  - Sensitivity analyses are conducted on a number of parameters, but these are varied one at a time, and no attempt is made to compare the cases where all parameters are at their extreme values.
  - As conducted, the sensitivity analyses are biased in favor of a positive impact of SNUS on population health.

Summary

The DPM (+1) structure is detailed and comprehensive as far as it goes, but it leaves out important elements, such as youth initiation and relationships with tobacco products other than cigarettes. More important, there are problems with the values of the parameters assumed in the

model and with omissions. These problems with the parameters in the model bias the results in favor of concluding a population benefit for SNUS.

Excess relative risk is a crucial parameter but is based on an older study reporting expert opinion and a comparison of lower nitrosamine Swedish SNUS to cigarettes. The transition rates in the model, including never tobacco-user to smoker or SNUS user, cigarette smoker to SNUS user or dual cigarette/SNUS user, and cigarette smoker to SNUS user to non-tobacco user are based on use studies – self-reported likelihood of use. Built into the model is the assumption that switching rates from cigarettes to SNUS will far exceed additional initiation rates of non-tobacco users. These assumptions all bias the results to show a population health benefit from SNUS marketing as an MRTP.

The model also omits a number of components that the FDA requires be included in assessing the benefit or harm of issuing an MRTP order. Morbidity is not measured in any way. Health risks to non-users of SNUS are not included but might include not only exposure to SNUS expectorate or product waste but also any increase in secondhand smoke exposure resulting from increased cigarette smoking related to SNUS use.

The DPM (+1) considers only cigarette use and ignores the possibility of SNUS users who switch from other tobacco products. E-cigarette use is increasingly popular and if e-cigarette users switch to SNUS, the excess relative risk would be much lower, possibly negative. Evidence suggests that many SNUS users will be dual or poly users. The DPM (+1) also omits any additional risk for dual users, assuming their mortality risk is the same as smokers.

RJR conducted sensitivity and tipping point analyses, but these analyses do not vary parameters across the full meaningful range of values and vary only one parameter at a time, which will lead to an underestimate of the true range of possible outcomes.

The DPM (+1) is biased in favor of finding a population health benefit for marketing SNUS as a MRTP. For the reasons outlined above, the FDA should not rely on the model as presented and should not grant a MRTP order for Camel SNUS products.

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