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Re: Docket No. FDA-2018-N-2066, Tobacco Products Scientific Advisory Committee; Notice of Meeting re R.J. Reynolds Modified Risk Applications for Camel Snus

The Campaign for Tobacco-Free Kids (Tobacco-Free Kids) submits these comments in connection with the upcoming meeting of the Tobacco Products Scientific Advisory Committee (TPSAC) to consider the above-referenced modified risk tobacco product applications for six Camel snus products, 83 Fed. Reg. 29125 (June 22, 2018). These are Preliminary comments meant to inform the discussion before TPSAC, but because the formal comment period is open and will not close until after the TPSAC meeting, and because the record that has been made available to the public is not complete, Tobacco-Free Kids reserves the right to submit more extensive comments on these applications prior to the close of the comment period.

These comments will address three central issues:

(1) The relationship between the modified risk applications that will be the subject of the TPSAC meeting and the pending FDA proposed rule that would establish a tobacco product standard for N-nitrosonornicotine (NNN) in finished smokeless tobacco products, including Camel snus;

(2) The statutory standards by which every Modified Risk Tobacco Application (MRTP) must be evaluated and the importance to public health of rigorous application of those standards; and

(3) The core empirical considerations that should govern TPSAC's consideration of the subject MRTP.

I. THE POTENTIAL IMPACT OF FDA'S PROPOSED NNN PRODUCT STANDARD FOR SMOKELESS TOBACCO ON THE PENDING CAMEL SNUS MODIFIED RISK APPLICATIONS

In the pending applications, R.J. Reynolds ("Reynolds") seeks authorization to market six Camel snus products as modified risk tobacco products. In general, Reynolds seeks to market these products with the claim that smokers who switch completely from cigarettes to Camel snus would reduce their risk of tobacco-related disease. However, on January 23, 2017, FDA published a proposed rule that would establish a limit of 1.0 microgram per gram of tobacco (on a dry weight basis) of N-nitrosonornicotine (NNN), a potent carcinogen, in all finished smokeless tobacco products, which would include Camel snus.[1] It is not clear from the pending applications whether the level of NNN in Camel snus exceeds the level allowable under the proposed rule[2] or how the adoption of a rule limiting NNN would otherwise impact an MRTP decision relating to Camel Snus if all smokeless products had to comply with the new rule.

There are several scenarios to consider. Should the proposed rule become final prior to FDA's disposition of the pending MRTPs for Camel snus, those applications would become moot if the Camel snus products do not conform to the new product standard. Should the proposed rule become final after an MRTP decision, if Camel snus does not comply, the product would need to be withdrawn. If the proposed rule becomes final and all smokeless products have to comply, including Camel snus, it is unclear how FDA would handle the MRTP for Camel snus.

FDA's proposed rule establishing a new product standard for NNN in smokeless tobacco products is amply supported by scientific evidence establishing that (1) NNN in smokeless tobacco is carcinogenic, (2) reducing the level of NNN in smokeless tobacco products marketed in the United States would substantially reduce the risk of oral cancers for users, and (3) conformance of smokeless tobacco to the proposed product standard is technically feasible as demonstrated by the presence on the U.S. market of Swedish snus products sold by Swedish Match that already meet the proposed standard.[3] Indeed, FDA estimates that in the 20 years following implementation of proposed product standard, approximately 12,700 new cases of oral cancer and approximately 2,200 oral cancer deaths would be prevented in the United States. During that 20-year period, approximately 15,200 life years would be gained were the standard to be put into effect.[4]

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1 Proposed Rule for Tobacco Product Standard for NNN level in Finished Smokeless Tobacco Products, 82 Fed. Reg. 8004 (January 23, 2017) (Proposed NNN rule).

2 *See* Reynolds Executive Summary, at 120, Figure 2.8.3-2.

3 *See generally,* Proposed NNN Rule, 82 Fed. Reg. at 8010-8026.

4 Proposed NNN Rule, 82 Fed Reg. at 8026.

In light of the substantial benefit to public health FDA anticipates from adoption of its proposed NNN standard, the proposed rule should be made final, and the standard implemented as soon as possible. The proposed rule was issued over eighteen months ago and the public comment period has been closed for over one year. There is simply no reason for FDA to further delay making the rule final. Once it does so, the pending MRTP applications for Camel snus may become moot, depending on whether Camel snus meets the product standard in the final rule. Thus, in addition to finalizing the proposed NNN product standard, FDA should require Reynolds to establish that Camel snus conforms to the standard before there are any further proceedings to consider the pending applications for those products. It makes little sense for FDA to consume its resources, including TPSAC's resources, in further consideration of the pending MRTP applications when they concern products that may no longer be permitted on the market.[5]

II. THE STATUTORY STANDARDS THAT SHOULD GOVERN TPSAC'S CONSIDERATION OF THE CAMEL SNUS MODIFIED RISK TOBACCO APPLICATION

The Family Smoking Prevention and Tobacco Control Act of 2009 (Tobacco Control Act or TCA) assigns TPSAC a unique and central role in FDA's assessment of modified risk applications. The involvement of TPSAC in evaluating modified risk products is mandatory under the TCA.[6] In providing its evaluation, it is essential that TPSAC have a full understanding of the tobacco industry's conduct that should inform FDA's application of the statutory standards.[7]

The Camel snus applications are governed by the standards set out in Section 911 of the Food, Drug and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act of 2009 (Section 911). Section 911 was enacted as a response to the tragic history of false and misleading tobacco industry claims that certain tobacco products were less

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[5] Of course, once the proposed NNN rule becomes final and is implemented, Reynolds will be free to pursue a new MRTP for any of its products that conform to the new NNN standard.

[6] *See* Section 911(f)(1) of the Food, Drug and Cosmetic Act, as amended by the Tobacco Control Act, provides that FDA "shall refer" to TPSAC "any application" for a modified risk order.

[7] Tobacco-Free Kids has addressed TPSAC's role in evaluating modified risk tobacco applications in multiple comments filed with FDA in recent years and incorporates those comments by reference. *See* Comments of Tobacco-Free Kids in Docket No. FDA-2017-N-0001, April 6, 2017 TPSAC meeting re review of modified risk applications (March 22, 2017); Comments of Tobacco-Free Kids, et al., in Docket No. FDA-2014-N-0001, April 18, 2014 TPSAC meeting re modified risk tobacco products (April 2, 2014; Comments of Tobacco-Free Kids, et al., Docket No. FDA-2013-N-0001-0056 re evaluation of risk and benefits of proposed modified risk tobacco products to population as whole (August 1, 2013); Comments of Tobacco-Free Kids in Docket No. FDA-2013-N-0001, April 30, 2013 TPSAC meeting re process for TPSAC consideration of modified risk tobacco product applications (April 23, 2013).

dangerous than other products that persuaded health-conscious consumers to switch to the "reduced risk" products instead of quitting altogether.

In enacting the Tobacco Control Act, Congress made specific findings about the potential harm to public health from modified risk claims that should guide FDA in its consideration of any modified risk product application. Congress found that "unless tobacco products that purport to reduce the risks to the public of tobacco use actually reduce such risks, those products can cause substantial harm to the public health. . . ." Sec. 2(37). Congress also found that "the dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk products are complete, accurate, and relate to the overall disease risk of the product." Sec. 2(40). Congress determined that it is "essential that manufacturers, prior to marketing such products, be required to demonstrate that such products will meet a series of rigorous criteria, and will 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." Sec. 2(36).

Under the Tobacco Control Act, a "modified risk tobacco product" is defined as a tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. A product is "sold or distributed" for such a use if, in relevant part,

> (1) [its] label, labeling, or advertising, either implicitly or explicitly [represents] that
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> > (i) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
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> > (ii) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
> >
> > (iii) the tobacco product or its smoke does not contain or is free of a substance, or…
>
> (3) the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the label, labeling, or advertising…that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or its free of, a substance or substances.

Thus, a modified risk product is defined in terms of the manufacturer's claims of reduced risk or reduced exposure in marketing the product, as well as its actions that may suggest to consumers that a product reduces risk or exposure to hazardous substances.

In evaluating an application under section 911, FDA must consider both the product itself and the modified risk claims sought to be made by the manufacturers. Even though a product may meet the standard for the grant of a marketing application, the manufacturer may not make reduced risk or reduced exposure claims unless FDA has granted a separate application under Section 911 authorizing the making of such claims pursuant to the standards set forth in that section. With respect to Swedish snus products marketed by Swedish Match North America, for example, FDA granted an application to market a number of new tobacco products,[8] but denied the manufacturer's application under section 911 to make the modified risk claims the company proposed in connection with the products.[9]

Under §911(g)(1), the burden is on the applicant seeking an order allowing the marketing of the product with a modified risk claim to demonstrate that the product "*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 population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." (emphasis added).

Sec. 911(g)(4) further requires FDA to take into account the following specific empirical factors in determining whether the (g)(1) standard has been met:

> (A) The relative health risks to individuals of the tobacco product that is the subject of the application;
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> (B) The increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the tobacco product that is the subject of the application;
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> (C) 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;
>
> (D) The risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation approved under chapter V to treat nicotine dependence.

Thus, FDA must consider not only the effects of the asserted modified risk product on those who use it, but also its population-wide impact on tobacco use initiation, cessation and relapse, including an assessment of the likelihood that smokers would actually switch to the modified risk product, given the claims made. It is not enough for an applicant to show that the product is less hazardous to users than other tobacco products; in order for a modified risk application to be

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[8] U.S. Food and Drug Administration, Premarket Tobacco Application (PMTA) Technical Project Lead (TPL) Review, Swedish Match North America, Inc. (Nov. 11, 2015).

[9] U.S. Food and Drug Administration, response letter from Benjamin J. Apelberg, CTP Office of Science to Swedish Match North America (Dec. 14, 2016).

granted, the applicant is required to show that the benefits of risk reduction to the individual (considering the likelihood of smokers switching to the modified risk product) outweigh the risks of increased initiation or diminished cessation. In short, the statute requires FDA to make scientific judgments not only about the physical effect of the product's use, but also about the likely responses of potential consumers (both smokers and non-smokers) to the product's marketing as a modified risk product.

III. CONSIDERATIONS RELATED TO TPSAC'S EVALUATION OF THE APPLICATION'S IMPACT ON THE INDIVIDUAL USER AND THE POPULATION AS A WHOLE

This portion of these comments is designed to inform TPSAC's consideration of this application in light of the statutory standards, based on the current science on the impact of using smokeless tobacco – particularly snus – at the individual and population level in the United States, as it affects switching from cigarette smoking to smokeless tobacco use, dual use of cigarettes and smokeless tobacco, and initiation of tobacco use.

A. Relevance of Scandinavian Epidemiological Evidence.

Reynolds frequently references evidence from Sweden to support its assertion that the products at issue will significantly reduce harm and the risk of tobacco-related disease to individuals. For instance, Reynolds asserts that the products under consideration in these applications present less risk compared to older versions of snus products marketed for many years in Sweden and that the epidemiological evidence from Sweden is therefore relevant to this evaluation.[10] However, although levels of toxicants in Swedish snus in past years were higher than they currently are,, it is not clear from the data submitted by Reynolds how long it has been since these levels in Swedish snus were comparable to current levels in Camel snus or how the presence of these toxicants in Swedish snus historically might have influenced the epidemiological results. Key parts of the application that describe Camel snus ingredients, including type of tobacco blend used and how it is made, have been redacted in the public version,[11] so we must depend on TPSAC and FDA to effectively evaluate whether or not any differences in contents or manufacturing processes between Camel snus and Swedish snus as marketed in the past are meaningful at the individual and population levels. It is clear, however, that levels of NNN and NNK in Camel snus exceed those in Swedish snus as it is currently marketed.

Reynolds relies heavily on epidemiological evidence from Scandinavia, where snus has been widely used for many decades. According to the applications, data from Sweden

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[10] See, e.g., Reynolds Executive Summary, at 91.

[11] See, e.g., Reynolds Executive Summary, at 89; Reynolds application section 3.1, at 2-4; and Reynolds application section 3.2, at 8-84.

demonstrates that Swedish snus is significantly less harmful than cigarettes, consumers' switching from cigarettes to snus have benefited the public health in those countries and, since Camel snus is a similar product, then the same must be true for the products under review.[12]

Because Swedish snus has been widely used in Sweden for many years, and because snus has constituted the vast majority of smokeless tobacco used in Sweden for many years, there exists a large data set for the evaluation of the health effects of Swedish snus in comparison with the health effects of cigarettes in Sweden. This experience has made possible the kind of "long, intensive and robust observational studies of actual health outcomes" referred to in the Institute of Medicine's 2012 report on *Scientific Standards for Studies on Modified Risk Tobacco Products*.

It is important to note, however, that this experience exists only with respect to health outcomes in Scandinavia involving the use of Swedish snus itself. Because product standards that restrict levels of certain components in Swedish snus have been in place in Sweden for decades, the experience that Reynolds cites may not translate for use of U.S. smokeless tobacco products, including Camel snus and other snus products sold by other manufacturers in the United States. For instance, snus sold in Sweden must comply with maximum levels of certain toxicants and carcinogens, but no such standard currently exists in the U.S.[13]

The risk posed by Swedish snus to individuals in Scandinavia is not necessarily identical to the risk posed by Camel snus to individuals in the United States. Although it seems apparent that completely switching from cigarettes to snus products would reduce health risks for smokers, the likelihood that U.S. consumers would switch completely is unknown because the products are not identical and because the patterns of use in the two countries are different.

There are factors that are likely to alter who uses these products in the U.S.; how they use them; and the relative risk that they will be used by non-smokers. For example, there are limitations to marketing tobacco products in Sweden that do not exist in the U.S., which could affect the impact of the proposed modified risk messages on users and potential users; unlike in Sweden, where advertising plays no role in the establishment of consumer preferences. Indeed, it is notable that Sweden has achieved high use rates for snus even without using these types of modified risk messages, because tobacco advertising in most media such as print advertisements and outdoor signage is not permitted in Sweden, though Internet and some point-of-sale advertising are allowed.[14] In the United States in 2016, the top five smokeless tobacco companies spent $759.3 million to advertise and market their products, increasing for the fourth year in a row, and more than triple the 2005 expenditures ($250.8 million), the year before

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[12] Reynolds Executive Summary, at 91.

[13] As noted above, however, FDA has proposed a rule that would set a maximum level of NNN in smokeless products.

[14] 14-14b §§ Tobakslag [Tobacco Act] (Svensk författningssamling [SFS] 1993:581) (Swed.), available at http://rkrattsbaser.gov.se/sfst?bet=1993:581. English version available at https://www.tobaccocontrollaws.org/files/live/Sweden/Sweden%20-%20SFS%202010727.pdf.

Reynolds acquired a smokeless tobacco company and began marketing its own smokeless tobacco products.[15] In addition, tobacco companies spent an additional $8.7 billion to market cigarettes in 2016[16] – showing that these companies, including Reynolds American, are not ready to give up cigarette smokers to smokeless tobacco any time soon.

This difference may well account for distinctions in the way snus is used in Sweden as compared to how it would be used in the United States. In the United States, where spending on marketing cigarettes is far higher than that for smokeless tobacco and smokeless tobacco use patterns are different, it is not surprising that the prevalence of dual use of smokeless tobacco and cigarettes has historically been higher than in Sweden.[17] Tobacco marketing plays an important role in attracting users – particularly youth. Tobacco companies have used a variety of strategies to entice youth to use smokeless tobacco: sweet and kid-friendly flavors, sponsorships of events popular with youth, advertisements with youth-oriented messages, and affordable prices.[18] The 2012 Surgeon General's report, Preventing Tobacco Use among Youth and Young Adults, found that the "integration of product design with marketing helped to reverse the mid-twentieth century decline in smokeless tobacco use and spurred a rapid increase in smokeless tobacco use by adolescents and young adult males."[19]

Further, the presence of other forms of smokeless tobacco that are more popular in the United States, but are not allowed in Sweden, could affect how Camel snus modified risk messages are perceived and may make the Swedish experience inapplicable to the U.S. For example, given the variety of smokeless tobacco products that are more popular than snus in the U.S., Camel snus' modified risk message might be easily lost or ignored by smokers, or, even worse, non-tobacco users may mistakenly believe that the modified risk message approved for Camel snus applies to other smokeless tobacco products and initiate use of these products, even though the risk profiles of such products are different. TPSAC needs to evaluate the impact of

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[15] U.S. Federal Trade Commission (FTC), *Smokeless Tobacco Report for 2016,* 2018, https://www.ftc.gov/system/files/documents/reports/federal-trade-commission-cigarette-report-2016-federal-trade-commission-smokeless-tobacco-report/ftc_smokeless_tobacco_report_for_2016_0.pdf. Data for top 5 manufacturers only: Altria Group, Inc.; North Atlantic Trading Company, Inc.; Reynolds American, Inc.; Swedish Match North America, Inc.; and Swisher International Group, Inc.

[16] FTC, *Cigarette Report for 2016*, 2018, https://www.ftc.gov/system/files/documents/reports/federal-trade-commission-cigarette-report-2016-federal-trade-commission-smokeless-tobacco-report/ftc_cigarette_report_for_2016_0.pdf [data for top 5 manufacturers only].

[17] Cheng, Y, et al., "Patterns of Use of Smokeless Tobacco in US Adults, 2013–2014," *American Journal of Public Health* 107(9):1508-1514, 2017. Lund, KE, McNeill, A, & Scheffels, J, "The use of snus for quitting smoking compared with medicinal products," *Nicotine & Tobacco Research* 12(8):817-22, August 2010, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2910876/pdf/ntq105.pdf. Tomar, S, Alpert, HR, & Connolly, GN, "Patterns of Dual Use of Cigarettes and Smokeless Tobacco Among US Males: Findings from National Surveys," *Tobacco Control* 19:104-109, 2010, http://tobaccocontrol.bmj.com/content/19/2/104.full.pdf+html. Agaku, IT, et al., "Use of Conventional and Novel Smokeless Tobacco Products Among US Adolescents," *Pediatrics* 132(3):e578-86, September 2013, http://pediatrics.aappublications.org/content/early/2013/07/31/peds.2013-0843.full.pdf.

[18] Campaign for Tobacco-Free Kids factsheet, Smokeless Tobacco and Kids, https://www.tobaccofreekids.org/assets/factsheets/0003.pdf.

[19] U.S. Department of Health and Human Services (HHS), *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*, 2012, at 539.

the modified risk designation for Camel snus independently of the Swedish experience, within the context of a market that includes other, more popular smokeless tobacco products that are sold here but are not present in Sweden.

Further, the historical Swedish data that Reynolds relied on did not include e-cigarettes because e-cigarettes did not have a meaningful presence in the marketplace at that time. In contrast, in the U.S., e-cigarettes are now heavily marketed and e-cigarette use is higher than snus (or smokeless tobacco) use among youth and adults.[20] Any consideration of Camel snus modified risk messages needs to account for the presence of e-cigarettes as another alternative to smoking.

Thus, while some of the longitudinal data from Sweden could be informative, TPSAC must consider the degree to which the references to the "Swedish experience" made by Reynolds applies to U.S. products and U.S. users given the different regulatory landscape. Indeed, in considering the modified risk application filed by Swedish Match for its Swedish snus products, TPSAC voted 6 votes "no," one vote "yes," and one abstention on this question: "Does the Committee believe that the epidemiological data from Sweden concerning tobacco use behavior provide relevant information on the likelihood that current tobacco users in the U.S. will switch to the use of these snus products?" Moreover, in the Swedish Match proceeding, TPSAC also cast 5 votes "no," with 3 abstentions, on the question: "Does the Committee believe that the epidemiological data from Sweden concerning tobacco use behavior provide relevant information on the likelihood that non-users of tobacco in the U.S. will initiate the use of these snus products?"

Finally, in its evaluation of the Swedish Match modified risk application, FDA found that the company had not demonstrated that "U.S. consumers would use Swedish snus in the same manner as consumers in Sweden and Norway (e.g. frequency or intensity of usage; exclusive use versus dual use with cigarettes); therefore, we cannot conclude that, as actually used by U.S. consumers, the products would substantially reduce the risk to smokers."[21] Although the conclusions reached by TPSAC and FDA in the Swedish Match proceeding do not bind the agency in the Camel snus proceeding, they counsel great caution in assessing Reynolds' claims based on the Swedish experience.

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[20] CDC, "Tobacco Use Among Middle and High School Students—United States, 2011-2017," *Morbidity and Mortality Weekly Report* (*MMWR)* 67(22):629-633, June 7, 2018, https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6722a3-H.pdf. Current use defined as any use in the past month. CDC, "Tobacco Product Use Among Adults — United States, 2015," *MMWR* 66(44):1209–1215, November 10, 2017, https://www.cdc.gov/mmwr/volumes/66/wr/pdfs/mm6644a2-H.pdf.

[21] FDA, *Modified Risk Tobacco Product (MRTP) Application Technical Project Lead (TPL) Review*, https://www.fda.gov/downloads/TobaccoProducts/Labeling/MarketingandAdvertising/UCM533233.pdf, November 2, 2016, at 10-11.

B. Importance of Determining How the Product Will Actually Be Used by Consumers.

TPSAC must consider how Camel Snus products under review, as "actually used by consumers," will impact both the risk to the individual and the risk to the population as a whole. Whether the product will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" may depend on the way the product is "actually used by consumers," and in evaluating the applicability of the Swedish experience on the marketing of the product in the United States, much may depend on whether the Camel Snus products will "actually be used" in the United States in the same manner as similar products were "actually used" in Sweden.

A substantial body of evidence supports the proposition that health benefits to an individual from quitting smoking occur only if the individual completely quits smoking. Merely reducing the number of cigarettes smoked or engaging in dual use of cigarettes and other tobacco products does not substantially reduce the health risk, as several U.S. Surgeon General's Reports and other studies have indicated that the risk of cardiovascular disease and other smoking-related diseases depends largely on the length of time a person smokes, not the number of cigarettes smoked.[22] According to the CDC, "If you only cut down the number of cigarettes you smoke by adding another tobacco product…you still face serious health risks. Smokers must quit smoking completely to fully protect their health – even a few cigarettes a day are dangerous."[23]

While *complete switching* to snus might "significantly" or "greatly" reduce smokers' risk of certain smoking-related diseases, as Reynolds states in its application, incomplete switching (dual use or merely cutting down smoking) keeps smokers' risks of disease elevated. Reynolds downplays this higher risk throughout its application, but one study concluded, "Because the health risks associated with cigarettes and ST are different in some respects, and because their effects may be additive if not synergistic, the concomitant use of cigarettes and ST may increase the risk of tobacco-attributable death and disease relative to use of either product alone."[24] Another, more recent study determined that reporting health issues was more likely among people who used both smokeless tobacco and cigarettes compared to those who used only one

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[22] U.S. Department of Health and Human Services (HHS), *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*, U.S. Centers for Disease Control and Prevention (CDC), Office of Smoking and Health (OSH), 2010, at 9. HHS, *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General,* CDC, OSH, 2012, at 22, http://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/index.html. Schane, RE, Ling, PM, & Glantz, SA, "Health Effects of Light and Intermittent Smoking: A Review," *Circulation* 121(3):1518-1522, 2010. Tverdal, A & Bjartveit, K, "Health Consequences of Smoking 1-4 Cigarettes per Day," *Tobacco Control* 14(5), 2005. Hackshaw, A, et al., "Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports," *BMJ* 360:j5855, http://doi.org/10.1136/bmj.j5855, 2018.

[23] CDC, "Powerful new Tips from Former Smokers" ads focus on living with vision loss and colorectal cancer," CDC Press Release, March 26, 2015, http://www.cdc.gov/media/releases/2015/p0326-tips.html. See also: CDC, "Dual Use of Tobacco Products." http://www.cdc.gov/tobacco/campaign/tips/diseases/dual-tobacco-use.html#ten.

[24] Wetter, D, et al., "Concomitant Use of Cigarettes and Smokeless Tobacco: Prevalence, Correlates, and Predictors of Tobacco Cessation," *Preventive Medicine* 34:638-648, 2002.

product.[25] TPSAC must weigh any reduction in risks due to reduced *exposure* to toxicants from incomplete switching against the known elevated risks due to continued smoking.

Dual or multiple product use is not a trivial concern in the U.S. According to Reynolds' application, "the vast majority of users of Camel Snus, non-Camel snus, portioned moist snuff, loose leaf chew and loose moist snuff are dual/poly users of other combustible and/or non-combustible tobacco products."[26] By contrast, most snus users in Sweden exclusively use snus.[27] It is important to differentiate the health risk data from Scandinavia between users who switch completely from cigarettes to snus and those who take up snus without completely giving up cigarettes.

Because of the critical difference in health outcomes for those who completely quit smoking when they take up snus and those who use cigarettes and snus concurrently, it is essential that any modified risk claims for snus include clear and understandable statements to consumers advising them that any health benefits depend upon their switching entirely away from cigarettes. Moreover, because of the difference in the disease risk presented by Camel snus and that presented by other smokeless tobacco products, any such claims should make it clear that health benefits depend on consumers not using other smokeless products as well. Failure to provide such information could mislead consumers into believing that dual use of snus and other tobacco products would confer a health benefit when in fact it would not.

Thus, TPSAC and FDA must carefully consider whether the modified risk claim that switching completely from cigarettes to Camel snus will significantly reduce disease risk sufficiently conveys the key message that the health benefits from switching depend on complete switching from cigarettes and on exclusive use of Camel snus vs. use of other smokeless tobacco products.

C. Evaluating the Individual Risks of Camel Snus

Although smokeless tobacco products do not present the same level of harm for users as cigarettes because smokeless tobacco is not burned, and snus presents a lower level of risk than other smokeless tobacco products, Camel snus still increase health risks compared to non-tobacco use. TPSAC should evaluate how the reduced exposure or risk from completely switching to Camel snus compares to the elevated risks from using Camel snus against non-smoking. Further, TPSAC should also consider that most smokers in the U.S. do not switch completely, and how that pattern of use impacts the level of risk to users.

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[25] Hernandez, SL, et al., "Relationships Among Chewing Tobacco, Cigarette Smoking, and Chronic Health Conditions in Males 18–44 Years of Age," *Journal of Primary Prevention* 38(5):505-514, 2017.

[26] Reynolds Executive Summary, at 168.

[27] Lund, KE & McNeill, A, "Patterns of Dual Use of Snus and Cigarettes in a Mature Snus Market," *Nicotine & Tobacco Research* 15(3):678-684, 2013.

1. Exposure to toxicants.

In a study looking at toxicity of Camel snus compared to FDA-approved nicotine gum among daily smokers, researchers found that Camel snus users (those who used only Camel snus and those who used Camel snus and continued to smoke) had higher levels of TSNAs compared to those who switched entirely to nicotine gum.[28]

Research has also shown that some Camel snus varieties contain higher levels of some toxicants compared to Swedish Snus,[29] which raises questions of how relevant the data provided by Reynolds in its applications are for U.S. users of Camel snus.

According to its applications submitted for Camel snus, Reynolds' own research found higher levels of NNK, NNN, nicotine, cadmium, and arsenic in Camel snus than in cigarettes.[30] Reynolds states that these higher levels in the products themselves may not translate into higher toxicant exposure when used,[31] but notes "that exclusive Camel Snus users exhibit reduced *or similar levels* of [TSNAs] when compared to cigarette smokers" [emphasis added], based in part on its own studies.[32]

2. Cardiovascular disease.

Recent studies have linked smokeless tobacco use with increases in the risk of death when users have heart attacks or strokes.[33] Two separate meta-analyses of studies found

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[28] Berman, ML, et al., "Consortium on Methods Evaluating Tobacco: Research Tools to Inform FDA Regulation of Snus," *Nicotine and Tobacco Research* [Epub ahead of print], doi: 10.1093/ntr/ntx228, October 4, 2017.

[29] Stepanov, I, et al., "New and traditional smokeless tobacco: comparison of toxicant and carcinogen levels," *Nicotine & Tobacco Research* 10(12):1773-1782, 2008; Stepanov, I, et al., "Increased Pouch Sizes and Resulting Changes in the Amounts of Nicotine and Tobacco-Specific N-Nitrosamines in Single Pouches of Camel Snus and Marlboro Snus," *Nicotine & Tobacco Research* 14(10):1241-5, 2012; Stepanov, I, 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):274-281, 2012; Stepanov, I, et al., "Monitoring Tobacco-Specific N-Nitrosamines and Nicotine in Novel Smokeless Tobacco Products: Findings From Round II of the New Product Watch," *Nicotine & Tobacco Research* 16(8):1070-1078, 2014. Swedish Match, *GOTHIATEK® limits for undesired components*, January 2018, accessed August 14, 2018, from https://www.swedishmatch.com/Snus-and-health/GOTHIATEK/GOTHIATEK-standard/. Hatsukami, D, et al., "Evidence Supporting Product Standards for Carcinogens in Smokeless Tobacco Products," *Cancer Prevention Research* 8(1):20-6, 2015.

[30] Reynolds Executive Summary, at 190.

[31] Reynolds Executive Summary, at 190-191.

[32] Reynolds Executive Summary, at 138. See also, comments by St. Helen, G, et al., 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," August 23, 2018, tracking number 1k2-9510-3zjn, available at https://tobacco.ucsf.edu/reynolds%E2%80%99-own-data-do-not-support-their-claim-because-exclusive-users-camel-snus-experience-lower-levels-exposure-some-toxicants-they-will-reduce-their-risk-harm-lung-cancer-oral-cancer-respiratory-disease-and-heart-disease.

[33] CDC, Smokeless Tobacco: Health Effects, December 1, 2016, https://www.cdc.gov/tobacco/data_statistics/fact_sheets/smokeless/health_effects/index.htm. NCI and CDC,

associations in risk of fatal myocardial infarction and fatal stroke among smokeless tobacco users.[34] Analysis of two surveys in Sweden found an association between snus use and an increased risk of heart failure.[35] The American Heart Association has also raised questions of an association between long-term smokeless tobacco use and higher risks of fatal myocardial infarctions and strokes.[36]

3. Oral Cancer.

In its denial of Swedish Match North America's modified risk tobacco product applications for eight General Snus products, FDA stated, "the totality of the scientific evidence supports the statement that smokeless tobacco products in general and these products in particular 'can cause mouth cancer…."[37]

A study looking at biomarker data from the Population Assessment of Tobacco and Health (PATH) survey found levels of oral carcinogen N'-nitrosonornicotine (NNN) in smokeless tobacco higher than in cigarettes at the same nicotine level.[38] In other words, when obtaining the same nicotine dose as cigarette smokers, smokeless tobacco users are exposing themselves to higher levels of NNN (and another carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)). Further, a meta-analysis found "evidence of elevated risk of HNC associated with snuff use among never cigarette smokers across various sets of adjustment variables and when analysis was restricted to cancers of the oral cavity."[39] These studies were not specific to snus. The majority of the products used in these studies are the traditional moist snuff products that expose users to higher levels of carcinogens compared to snus products. An examination of just snus products might conceivably produce a different outcome.

A study comparing the health effects of U.S. smokeless tobacco products compared to Swedish Snus in Scandinavia found that while the use of Swedish snus did not increase the risk

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Smokeless Tobacco and Public Health: A Global Perspective, Bethesda, MD: HHS, CDC, NIH, NCI, NIH Publication No. 14-7983, December 2014, http://cancercontrol.cancer.gov/brp/tcrb/global-perspective/index.html.

[34] Boffeta, P & Straif, K, "Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis," *BMJ*, 339: b3060, 2009, http://www.ncbi.nlm.nih.gov/pubmed/19690343. Vidyasagaran, AL, Siddiqi, K, & Kanaan, M, "Use of smokeless tobacco and risk of cardiovascular disease: A systematic review and meta-analysis," *European Journal of Preventive Cardiology* 23(18):1970-1981, 2016.

[35] Arefalk, G, et al., "Smokeless tobacco (snus) and risk of heart failure: results from two Swedish cohorts," *European Journal of Preventive Cardiology* 19(5):1120-27, 2012, http://www.ncbi.nlm.nih.gov/pubmed/21828223.

[36] Piano, MR, "Impact of Smokeless Tobacco Products on Cardiovascular Disease: Implications for Policy, Prevention, and Treatment. A Policy Statement from the American Heart Association," *Circulation* 122(15):1520-44, October 12, 2010.

[37] FDA, *Modified Risk Tobacco Product (MRTP) Application Technical Project Lead (TPL) Review*, https://www.fda.gov/downloads/TobaccoProducts/Labeling/MarketingandAdvertising/UCM533233.pdf, November 2, 2016, at 10.

[38] Chaffee, BW & Benowitz, N, "Nicotine and Carcinogen Exposure by Tobacco Product Type and Dual-Use," Poster presented at the 96th General Session of the International Association for Dental Research (IADR), July 2018.

[39] Wyss, AB, et al., "Smokeless Tobacco Use and the Risk of Head and Neck Cancer: Pooled Analysis of US Studies in the INHANCE Consortium," *American Journal of Epidemiology* 184(10):703-716, 2016.

of oral cancer in Scandinavia compared to non-tobacco use, the smokeless products sold in the United States did increase oral cancer risk among users in the United States compared to non-tobacco use.[40] Thus, whatever conclusion might be drawn from the epidemiological evidence regarding the effect of Swedish snus on users in Scandinavia is not generalizable to other smokeless tobacco products and particularly not to the use of other smokeless tobacco products in the United States, including products sold by other companies as "snus" in the United States.

D. Evaluating Population-Level Risks of Camel Snus

Data related specifically to snus use in the United States are limited due to the very low use rate. Most of the relevant data in the U.S. assess consumer behavior with respect to the broad smokeless tobacco category that includes snus, dry and moist snuff and chewing tobacco, and of which moist snuff makes the largest portion. TPSAC should evaluate the appropriateness of a modified risk designation for these Camel snus products based on the available evidence on consumer behavior patterns with smokeless tobacco products in the U.S., not purely on the Swedish experience with snus, which is unlikely to be replicated in the U.S. TPSAC should also consider the impact of the modified risk messaging for Camel snus with respect to the use of other smokeless tobacco products, and if the possible impacts would be beneficial or harmful at the population level.

1. Importance of Determining if a Modified Risk Marketing Order for the Product Will Benefit the Population as a Whole.

In order to obtain a modified risk marketing order, the applicant must also demonstrate that the issuance of such an order would "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." Demonstrating such a benefit requires a prediction of the effect of the proposed claim on consumer behavior. Assuming that an individual who smokes cigarettes or uses another smokeless tobacco product and switches to Camel Snus as a result of the modified risk claim receives a significant health benefit, such benefits would be offset by (1) individuals who might otherwise have quit smoking or using other smokeless tobacco products engaging in dual use as a result of the claims; (2) individuals who have never used tobacco products initiating with snus as a result of the claims; and (3) individuals who have quit using tobacco products re-initiating with snus as a result of the claims. Thus, it becomes necessary to predict the effect of such claims on each potential group.

While the public should receive truthful information about the relative risk of tobacco products, efforts must be made to make sure those messages are not misunderstood or create unintended consequences. Considering data showing that youth smokeless tobacco users already

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[40] Hatsukami, D & Stepanov, I, *Establishing product standards for smokeless tobacco*, report included with comments submitted by the Campaign for Tobacco-Free Kids and the Tobacco Control Legal Consortium to Docket No. FDA-2014-N-1051, November 25, 2014, https://www.regulations.gov/document?D=FDA-2014-N-1051-0829, at 28-29.

view the health risks from smokeless tobacco use as less severe compared to non-users,[41] there needs to be a balance between providing this information to encourage smokers to switch completely and portraying the information in such a way that non-users, particularly youth, believe that using smokeless tobacco is worth the health risk. This entails not only pre-review of messages, but also post-market evaluations.

One potentially significant effect should also be considered: in addition to considering the benefits from smokers who otherwise would not have quit switching completely to Camel Snus, there would also likely be a population-wide benefit from users of other smokeless tobacco products switching to Camel Snus. While this population is much smaller than that of smokers, given evidence that users of traditional smokeless tobacco products are more aware of snus than non-users,[42] the prospect of a complete switch to Camel Snus might be higher.

For all these reasons, a determination of the effect of Reynolds' proposed claims must depend principally on studies of consumer perception and consumer behavior in the United States. In evaluating this application, several issues should be considered as they pertain to consumer perception and behavior.

1. The effects of the specific claims to be made must be considered. The language of any specific claim and the method by which it is to be disseminated must be studied to make sure consumers fully understand the importance of complete switching and the degree of the reduced risk. Moreover, the means by which a modified risk claim is disseminated would also be relevant in such an analysis. A claim made in a major advertising campaign in numerous media outlets might well have a different effect from a claim made by posting signs at the point of sale. Both the message and the means of delivery must be considered.

Claims should be considered in light of the population they are designed to target. The population as to which a modified risk claim should be addressed is existing users of cigarettes, other combusted tobacco products, or other smokeless tobacco products. The effectiveness with which such a claim is targeted to this population may affect the appropriateness of granting the application. Thus, *to truly benefit the population, the applicant must adequately show that the message and design of its marketing materials, as well as its dissemination plan, is targeted exclusively to current smokers and users of tobacco products, and exposure to youth and non-tobacco users is limited.* In any event, consideration of any modified risk claim should take into account the population actually most likely to encounter the claim, as opposed to the population intended to encounter the claim.

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41 Couch, ET, et al., "Smokeless Tobacco Decision-Making Among Rural Adolescent Males in California," *Journal of Community Health* 42(3):544-550, 2017.

42 Biener L, et al., "Snus Use and Rejection in the United States," *Tobacco Control* 25(4):386-392, 2016.

2. Any claim should include sufficient information to avoid misleading or confusing consumers. Because the benefits of switching from cigarettes or other smokeless tobacco products to Camel snus accrue only to the extent that consumers who otherwise would not quit switch to this product exclusively, adequate testing must be done to ensure that any modified risk claim clearly and explicitly communicates this message in a way that is fully understood by the public.

3. Camel snus presents a very different health risk to an individual than that presented by other smokeless tobacco products, particularly the traditional moist snuff products that are popular in the U.S. Reynolds suggests in its applications that, over time, exposure to the modified risk statements from Camel Snus will influence perceptions of relative risk among overall smokeless tobacco products compared to cigarettes, stating, "Indeed, education about relative risks of smokeless tobacco and snus versus smoking (in the form of Camel Snus modified risk advertising) has the potential to mitigate the prevailing misperceptions about relative risk of smokeless tobacco versus cigarettes."[43] However, to the extent that the proposed Camel snus modified risk claims influence perceptions of risk for other smokeless tobacco products, this may lead, for example, to a greater risk of initiation of those other products.

For instance, Reynolds American also markets Grizzly moist snuff tobacco, which has the second highest market share in Nielsen-tracked channels[44] and in 2014 (the most recent available), it was most popular smokeless tobacco brand among 12-17 year olds.[45] The health risks associated with Grizzly products are different than those from Camel snus. Thus, TPSAC should make sure that Reynolds has properly evaluated whether or not the use of modified risk messages in Camel snus marketing would affect the use of Grizzly or other smokeless tobacco products, particularly among youth and other vulnerable populations.

4. Although general education about the relative risk of smokeless tobacco compared to cigarettes is important, comprehension of the statement still needs to be considered for nonsmokers, particularly youth. Reynolds states in its application that the company "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."[46] However, given the history of tobacco companies misleading the public on "light" and "low-tar" cigarettes, and marketing to youth to increase product sales, the worst-case, and perhaps more likely, scenario would be if youth and nonsmokers misunderstand the

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43 Reynolds Executive Summary, at 85.

44 Wells Fargo Securities, *Nielsen: Tobacco All Channel Data Thru 6/16*, June 26, 2018.

45 U.S. Department of Health and Human Services (HHS), SAMHSA Center for Behavioral Health Statistics and Quality, *National Survey on Drug Use and Health*, 2014. ICPSR36361-v1, Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], 2016-03-22, http://doi.org/10.3886/ICPSR36361.v1.

46 Reynolds Executive Summary, at 85.

message and believe that Camel snus and other smokeless tobacco products are "safe" to start using, but then become addicted to nicotine and switch to smoking cigarettes or other combustible products.

2. Would a Modified Risk Claim Result in Increased Smoking Cessation?

Camel snus currently has relatively low use rates in the U.S. compared to traditional smokeless tobacco products, and it is questionable if a modified risk designation will increase its use by smokers who plan to switch completely, or if those smokers will use Camel snus in addition to smoking cigarettes. TPSAC should determine, based on available U.S. data, experiences, alternative products on the market, and current regulatory structures, if smokers will actually switch completely to Camel snus.

Despite the data from Sweden presented by Reynolds, there is not sufficient evidence in the U.S. on the impact of smokeless tobacco in helping smokers quit to support an inference that there would be a similar effect in the U.S. The 2008 Update of the U.S. Public Health Service Clinical Practice Guidelines regarding tobacco cessation concluded, "the use of smokeless tobacco products is not a safe alternative to smoking, nor is there evidence to suggest that it is effective in helping smokers quit."[47]

Unlike the Swedish evidence, evidence in the U.S. does not indicate that smokers would switch to exclusive smokeless tobacco use (i.e., the evidence does not demonstrate that smokers who take up smokeless tobacco would abstain from smoking cigarettes). U.S. smokers do not prefer to use smokeless tobacco, even snus, to quit smoking. A recent study showed that daily smokers were no more likely to stop smoking for 7 days with Camel snus compared to with FDA-approved nicotine gum. The study authors stated, "Snus (with levels of nicotine similar to nicotine gum) was no better than nicotine gum in sustaining abstinence from smoking, but was significantly more toxic."[48] Older data on smokers' attitudes about switching to smokeless

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[47] Fiore, MC, et al., *Treating Tobacco Use and Dependence: 2008 Update*, U.S. Public Health Service Clinical Practice Guideline, May 2008, http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf.

[48] Berman, ML, et al., "Consortium on Methods Evaluating Tobacco: Research Tools to Inform FDA Regulation of Snus," *Nicotine and Tobacco Research* [Epub ahead of print], doi: 10.1093/ntr/ntx228, October 4, 2017, https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/ntx228/4331541.

tobacco confirm this finding.[49] Even among adult smokers given free Camel snus and who used the products beyond experimentation found them to be "poor substitute[s] for cigarettes."[50]

Instead, in the U.S., smokeless tobacco users were more likely to switch to cigarettes. One U.S. longitudinal study found that few male smokers stopped smoking and switched to smokeless tobacco (0.3 percent in one year) and few former smokers turned to smokeless tobacco (1.7 percent), and concluded that "smokeless tobacco is less useful for quitting smoking among U.S. smokers because in all likelihood they would quit smokeless tobacco before they quit cigarettes."[51] Another longitudinal study of adolescent and young adult males who were smokers at baseline but did not use smokeless tobacco found that at four-year follow-up less than one percent (0.8 percent) switched to smokeless tobacco and 3.6 percent continued to smoke and became smokeless tobacco users as well.[52]

In a study of smokers who did not intend to quit, among those who chose to use the provided snus product (Camel snus), more frequent and regular use were found to help prompt quit attempts and abstinence. However, this was a small minority of participants in the study. The researchers had provided some brief information about "why it [snus] might be considered safer than cigarettes" but did not provide instructions on how to use the products. The researchers indicated that providing snus without education about how to use the product could undermine quit attempts.[53] TPSAC should consider whether or not, as part of the modified risk statements proposed by Reynolds, the company should also include more explicit instructions on how to properly use Camel snus to increase the likelihood that smokers would continue to use it and switch from cigarettes.

Other evidence suggests that smokers in the U.S. prefer to use pharmaceutical nicotine products to quit over smokeless tobacco products. The previously mentioned study comparing preference for Camel snus to FDA-approved nicotine gum found that "When provided the option between snus and nicotine gum, current smokers appear to gravitate towards the less harmful

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[49] A 2009 study based on data from the California Tobacco Survey showed that the majority of daily smokers were not interested in switching their cigarettes for smokeless tobacco. In fact, 87 percent of smokers said they were "definitely not" or "probably not" open to the idea of replacing their cigarettes with smokeless tobacco, compared to only 12.7 percent of the smokers who reported that they "definitely" or "probably" would consider it. [Timberlake, D, "Are smokers receptive to using smokeless tobacco as a substitute?" *Preventive Medicine* 49(2-3):229-32, 2009, http://www.ncbi.nlm.nih.gov/pubmed/19631684.] A national cross-sectional study of current and former smokers found that just "7.8% of respondents reported that they tried to quit smoking by switching to chewing tobacco, snuff, or snus; an additional 5.8% considered it but never tried, and most never considered it." [Popova, L & Ling, PM, "Alternative Tobacco Product Use and Smoking Cessation: A National Study," *American Journal of Public Health* 103(5):923-930, May 2013, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3661190/pdf/nihms456593.pdf.]

[50] Meier, E, et al., "Perceptions of Snus Among US Adult Smokers Given Free Product," *Nicotine & Tobacco Research* 20(1):22-29, 2018.

[51] Zhu, S-H, et al., "Quitting Cigarettes Completely or Switching to Smokeless: Do U.S. Data Replicate the Swedish Results?," *Tobacco Control* 18:82-87, 2009, at 86.

[52] Tomar, S, "Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. experience," *Nicotine & Tobacco Research* 5(4):561-569, August 2003, http://www.ncbi.nlm.nih.gov/pubmed/12959794.

[53] Carpenter, MJ, et al., "Snus undermines quit attempts but not abstinence: a randomised clinical trial among US smokers," *Tobacco Control* 26(2):202-209, 2017.

nicotine gum as a preferred alternative to cigarettes."[54] Older studies of smokers have found similar preferences for nicotine replacement products over smokeless tobacco.[55]

Another major consideration is that the popular smokeless tobacco products in the U.S. are traditional moist snuff, not snus. Even though Camel snus has the highest market share among snus products sold in the U.S., that overall snus market is quite low. Convenience store data show that snus products made up less than five percent of smokeless tobacco unit sales through 2016, and of the snus brands, Camel products were the most shipped brands.[56]

While there may be some experimentation of snus, regular use of snus use is very low among adults and youth. In 2012, current snus use was 0.8 percent among middle school students and 2.5 percent among high school students.[57] A separate national survey of 2013-2014 data found 0.5 percent of youth (12-17 years old) were current snus users.[58] More recent youth surveys include snus within the smokeless category. Only 5.4 percent of U.S. adults had ever used snus in 2012-2013 and among current snus users, only 11.3 percent report using the product every day.[59] PATH data from 2013-2014 found that less than one percent of adults were current snus users.[60]

3. Would a Modified Risk Claim Result in Increased in Dual Use?

The question of whether smokers who take up smokeless tobacco switch completely and abstain from smoking entirely or whether they use both products concurrently (dual use) has extremely important health consequences. As mentioned previously, dual use may prolong duration of smoking, which plays a major role in increasing risks of developing smoking-related diseases.[61] Thus, TPSAC must assess whether smokers who take up a smokeless tobacco

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[54] Berman, ML, et al., "Consortium on Methods Evaluating Tobacco: Research Tools to Inform FDA Regulation of Snus," *Nicotine and Tobacco Research* [Epub ahead of print], doi: 10.1093/ntr/ntx228, October 4, 2017, https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/ntx228/4331541.

[55] O'Connor, RJ, et al., "US smokers' reactions to a brief trial of oral nicotine products," *Harm Reduction Journal* 8:1-10, 2011, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3032705/pdf/1477-7517-8-1.pdf. Shiffman, S, et al., "Smokers' Preferences for Medicinal Nicotine vs Smokeless Tobacco," *American Journal of Health Behavior* 31(5):462-472, September/October 2007, http://www.ncbi.nlm.nih.gov/pubmed/17555377.

[56] "Tobacco: Smokeless," *Convenience Store/Petroleum Category Management Handbook* 2017, http://digitaledition.qwinc.com/publication/?i=399534#{%22issue_id%22:399534,%22page%22:54}, at 53, 54.

[57] CDC, "Tobacco Product Use Among Middle and High School Students — United States, 2011 and 2012," *MMWR* 62(45):893-897, November 15, 2013, http://www.cdc.gov/mmwr/pdf/wk/mm6245.pdf.

[58] Kasza, KA, et al., "Tobacco-Product Use by Adults and Youths in the United States in 2013 and 2014," *New England Journal of Medicine* 376(4):342-353, 2017.

[59] CDC, "Tobacco Product Use Among Adults — United States, 2012–2013," *MMWR* 63(25):542-547, June 27, 2014, http://www.cdc.gov/mmwr/pdf/wk/mm6325.pdf.

[60] Cheng, Y, et al., "Patterns of Use of Smokeless Tobacco in US Adults, 2013–2014," *American Journal of Public Health* 107(9):1508-1514, 2017. Kasza, KA, et al., "Tobacco-Product Use by Adults and Youths in the United States in 2013 and 2014," *New England Journal of Medicine* 376(4):342-353, 2017.

[61] U.S. Department of Health and Human Services (HHS), *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*, U.S. Centers for Disease Control and Prevention (CDC), Office of Smoking and Health (OSH), 2010, at 9. HHS, *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General,* CDC, OSH, 2012, at 22, http://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/index.html. Schane, RE, Ling, PM, & Glantz, SA, "Health Effects of Light and Intermittent

product will actually use that product (i.e., whether they would use it exclusively while abstaining from smoking or whether they would use both products concurrently) to determine if there is any potential benefit to health that might result from approval of a modified risk application.

Smokers may try snus for various reasons, including to reduce their smoking, but they more often end up using both products rather than switching completely.[62] Several studies have found that dual users have similar or lower likelihood of quitting or attempting to quit smoking compared to exclusive cigarette smokers.[63] One study has found that, while dual users were more likely to make a quit attempt compared to exclusive smokers, they tended to relapse more quickly compared to exclusive smokers, and had comparable 30-day abstinence levels to exclusive smokers.[64] U.S. smokers perceive snus as a temporary replacement, not a complete substitution for cigarettes,[65] and dual users of smokeless tobacco and cigarettes use smokeless tobacco to maintain their cigarette addiction, not to quit smoking,[66] and do not believe that smokeless products can help them quit smoking.[67] One study found that smokeless users who used these products to cut down on smoking were no more likely to stop using cigarettes compared to those smokers who did not use smokeless tobacco,[68] and another study found that smokers saw these products as temporary, rather than complete substitutes.[69]

Smoking: A Review," *Circulation* 121(3):1518-1522, 2010. Tverdal, A & Bjartveit, K, "Health Consequences of Smoking 1-4 Cigarettes per Day," *Tobacco Control* 14(5), 2005. Hackshaw, A, et al., "Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports," *BMJ* 360:j5855, http://doi.org/10.1136/bmj.j5855, 2018.

[62] Biener L, et al., "Snus Use and Rejection in the United States," *Tobacco Control* 25(4):386-392, 2016, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4519419/pdf/nihms707341.pdf.

[63] Schauer, GL, Pederson, LL, & Malarcher, AM, "Past Year Quit Attempts and Use of Cessation Resources Among Cigarette-Only Smokers and Cigarette Smokers Who Use Other Tobacco Products," *Nicotine & Tobacco Research* 18(10):41-47, 2016. Klesges, RC, et al., "Tobacco Use Harm Reduction, Elimination, and Escalation in a Large Military Cohort," *American Journal of Public Health* 100(12):2487-2492, December 2010, at 2490 ("Importantly, dual users were less likely to become tobacco abstinent than were smokers or smokeless tobacco users . . . ."); Wetter, D, et al., "Concomitant Use of Cigarettes and Smokeless Tobacco: Prevalence, Correlates, and Predictors of Tobacco Cessation," *Preventive Medicine* 34:638-648,2002, ("Concomitant users were significantly less likely to quit using tobacco over the course of 4 years than were users of cigarettes or ST.").

[64] Messer, K, et al., "Cigarette smoking cessation attempts among current US smokers who also use smokeless tobacco," *Addictive Behaviors* 51:113-119, 2015.

[65] Bahreinifar, S, Sheon, NM, & Ling, PM, "Is snus the same as dip? Smokers' perceptions of new smokeless tobacco advertising," *Tobacco Control* 22:84-90, 2013, http://tobaccocontrol.bmj.com/content/22/2/84.

[66] McClave-Regan, AK & Berkowitz, J, "Smokers who are also using smokeless tobacco products in the US: a national assessment of characteristics, behaviours and beliefs of 'dual users'," *Tobacco Control* 20:239-242, 2011, http://www.ncbi.nlm.nih.gov/pubmed/21172853.

[67] McClave-Regan, AK & Berkowitz, J, "Smokers who are also using smokeless tobacco products in the US: a national assessment of characteristics, behaviours and beliefs of 'dual users'," *Tobacco Control* 20:239-242, 2011.

[68] Kasza, KA, et al., "Cigarette Smokers' Use of Unconventional Tobacco Products and Associations With Quitting Activity: Findings From the ITC-4 U.S. Cohort," *Nicotine & Tobacco Research* 16(6):672-681, June 2014, http://www.ncbi.nlm.nih.gov/pubmed/24376276.

[69] O'Connor, RJ, et al., "US smokers' reactions to a brief trial of oral nicotine products," *Harm Reduction Journal* 8:1-10, 2011, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3032705/pdf/1477-7517-8-1.pdf.

Studies from the years before e-cigarettes became popular show an increase dual use of smokeless tobacco and cigarettes,[70] and Minnesota Adult Tobacco survey data show that the increase in smokeless tobacco use was largely due to current smokers using smokeless tobacco concurrently, not to smokers switching to smokeless tobacco.[71] Survey data show that multiple tobacco product use is common among youth and adult tobacco users,[72] and before e-cigarettes, dual use of smokeless tobacco and cigarettes was popular.[73] Data from the NIH and FDA-funded Population Assessment of Tobacco and Health (PATH) study from 2013-2014 survey found that there were more current snus users also using other tobacco products than exclusive snus users.[74] Moreover, snus users were "more likely to report…polytobacco use than users of other SLT [smokeless tobacco] products."[75]

Reynolds' own application, referencing its own survey data and PATH data, found that "Greater than 90% of Camel Snus users are dual/poly users of other combustible and/or non-combustible tobacco products."[76] Separate analysis of 2013-2014 PATH data show that 42.6 percent of adult cigarette smokers were snus users, compared to 27.7 percent of former smokers and 29.7 percent of never smokers who reported currently using snus.[77]

These findings are not that surprising given that in the U.S., many new smokeless tobacco products have been marketed as a way to get a nicotine fix when smokers cannot smoke. Early marketing for Camel Snus used that precise message: One newspaper ad stated, "Snusing is allowed in the following places: In a **bar**, on a boat, or in your car. … Pleasure for Wherever" (emphasis in original),[78] while a point-of-sale pamphlet stated, "Enjoy Snus: Anytime,

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[70] Rath, JM, 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(679134):1-9, 2012, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3361253/pdf/JEPH2012-679134.pdf. Boyle, R, et al., "Concurrent Use of Cigarettes and Smokeless Tobacco in Minnesota," *Journal of Environmental and Public Health,* 2012.

[71] Boyle, R, et al., "Concurrent Use of Cigarettes and Smokeless Tobacco in Minnesota," *Journal of Environmental and Public Health,* (2012).

[72] Kasza, KA, et al., "Tobacco-Product Use by Adults and Youths in the United States in 2013 and 2014," *New England Journal of Medicine* 376(4):342-353, 2017.

[73] Substance Abuse and Mental Health Services Administration (SAMHSA), *The NSDUH Report: Smokeless Tobacco Use, Initiation, and Relationship to Cigarette Smoking: 2002 to 2007*, Rockville, MD: Office of Applied Studies, March 5, 2009, at 5. Tomar, SL, "Patterns of Dual Use of Cigarettes and Smokeless Tobacco among U.S. Males: Findings from National Surveys," *Tobacco Control* 19:104-109, 2010, at 105. Rath, JM, 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(679134):1-9, 2012, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3361253/pdf/JEPH2012-679134.pdf.

[74] Cheng, Y, et al., "Patterns of Use of Smokeless Tobacco in US Adults, 2013–2014," *American Journal of Public Health* 107(9):1508-1514, 2017.

[75] Cheng, Y, et al., "Patterns of Use of Smokeless Tobacco in US Adults, 2013–2014," *American Journal of Public Health* 107(9):1508-1514, 2017.

[76] Reynolds Executive Summary, at 109.

[77] Cheng, Y, et al., "Patterns of Use of Smokeless Tobacco in US Adults, 2013–2014," *American Journal of Public Health* 107(9):1508-1514, 2017, at 1513.

[78] Camel snus ad in *The Austin Chronicle*, October 13, 2006, available at http://www.trinketsandtrash.org/detail.php?artifactid=6792.

Anywhere! It's Limitless!"[79] Such marketing discourages smokers from taking the one step that is sure to protect their health, which is to quit smoking entirely. These types of messaging could undermine any modified risk statement about "switching completely," so TPSAC must evaluate the proposed statements in the context of other smokeless tobacco marketing.

Reynolds downplays the health risks of dual use and cites two studies to claim that dual use of smokeless tobacco and cigarettes does not raise "unique health risks" separate from exclusive use of either product, and even that dual use shows "somewhat reduced risks."[80] It is important to note that one of the studies cited in the application was published by researchers working for Altria, and the other was funded by Altria and Swedish Match – companies that have a financial interest in increasing the use of smokeless tobacco, and, in the case of Altria, also maintaining the use of cigarettes. In 2009, Altria had marketed its own Marlboro Snus products in "convenient foilpack[s]" that "ride[s] perfectly alongside your smokes" because they were slim enough to fit inside cigarette packs.[81] It remains in the company's best interest to publish studies that minimized health risks from dual use.

Of the limited studies of Camel snus in the U.S. available, some show that smokers have little interest in Camel snus,[82] even with a modified risk message.[83] TPSAC should consider whether or not a modified risk message – which could be misinterpreted by non-smokers, especially youth – would have an impact on smokers, especially since Camel snus is no more effective in helping smokers completely switch than FDA-approved nicotine gum, yet exposes them to more toxicants.[84]

4. How Likely Would Those Exposed to Modified Risk Messages Initiate Smokeless Tobacco Use or Transition from Smokeless Tobacco Use to Smoking?

When Camel snus was first introduced, news reports indicated that it was popular among high school students because of its concealable nature. One news article from that time described a high school student admitting to using Camel snus during class, who said, "It's easy, it's super-discreet…and none of the teachers will ever know what I'm doing."[85] Given that

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[79] Camel snus point of sale pamphlet, 2008, available at http://www.trinketsandtrash.org/detail.php?artifactid=5888.

[80] Reynolds Executive Summary, at 131.

[81] Marlboro Snus website, screenshots taken April 16, 2009.

[82] Carpenter, MJ, et al., "Snus undermines quit attempts but not abstinence: a randomised clinical trial among US smokers," *Tobacco Control* 26(2):202-209, 2017. Biener L, et al., "Snus Use and Rejection in the United States," *Tobacco Control* 25(4):386-392, 2016.

[83] Berman, ML, et al., "Consortium on Methods Evaluating Tobacco: Research Tools to Inform FDA Regulation of Snus," *Nicotine and Tobacco Research* [Epub ahead of print], doi: 10.1093/ntr/ntx228, October 4, 2017.

[84] Hatsukami, D, et al., "Randomised clinical trial of snus versus medicinal nicotine among smokers interested in product switching," *Tobacco Control* 25:267-274, 2016.

[85] Nelson, L, "If you think Snus is a safe alternative to smoking, think again," *Kansas City Star*, October 31, 2007.

smokeless tobacco rates among youth have not declined as rapidly as cigarette smoking, [86] it is important that TPSAC carefully review any data on the impact of expanding Camel snus marketing with a modified risk message on youth initiation, including a possible gateway effect to smoking and dual use. Because the consumer perception studies and the "likelihood of use" studies submitted by Reynolds as part of its application did not include youth, a complete assessment of the impact of the modified risk statement cannot be made by TSPAC or FDA.

FDA's assessment of Reynolds' MRTP applications must consider the population-wide impact of the products on both users and non-users of tobacco products, which includes its impact on tobacco use initiation. Both FDA's Guidance for the preparation of Modified Risk Tobacco Product Applications and Institute of Medicine's (IOM) 2012 report, *Scientific Standards for Studies on Modified Risk Tobacco* recommend or even require the inclusion of youth in consumer perceptions studies of promotional material to determine the effect of such modified risk claims on adolescent risk perception or interest in using the product.[87] Given that adolescence is a period of heightened vulnerability for the initiation of tobacco use, it is important to evaluate whether adolescents accurately understand the purported benefits of an MRTP. Of particular importance are adolescents' perceptions of the risks and benefits of using the product, and whether they intend to initiate tobacco use with the MRTP rather than a traditional tobacco product because they believe the former is a "safe" alternative."[88] Reynolds' failure to provide any evidence of the effect of these messages on adolescent risk perception is an inexplicable omission, against FDA's express instructions. The need to consider the effects of promotional statements on youth is vitally important in light of the industry's documented history of marketing tobacco products in ways that attract adolescents and the role that youth initiation has played—and continues to play—in the recruitment of long-term adult smokers.[89]

FDA's guidance on MRTP applications and IOM's report describe how such research should be done. Recognizing that research among non-smokers, and non-smoking youth in particular, requires care, FDA offered applicants an opportunity to work with the agency to determine the best way to conduct studies involving youth. [90] IOM suggested that such research could be appropriately done under the supervision of an independent third party.[91]

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86 CDC, "Tobacco Use Among Middle and High School Students—United States, 2011-2017," *Morbidity and Mortality Weekly Report (MMWR)* 67(22):629-633, June 7, 2018.

87 FDA Draft Guidance, Modified Risk Tobacco Applications, March 2012, at 20.

88 Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products*, December 2011, ("IOM report") at 165.

89 U.S. Department of Health and Human Services (HHS), *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012, at 530-41, 603-27 and sources cited therein; *U.S. v. Philip Morris*, 449 F. Supp. 2d at 561-691.

90 FDA 2012 Draft Guidance, at 26. IOM report at 7, 14, 50.

91 IOM report at 57.

TPSAC should evaluate whether an application that presents no evidence on the effect of modified risk claims on youth initiation or perception of risk can possibly meet the public health standard.

Available U.S. prevalence surveys do not provide a lot of detail on snus use among youth, but even data on general smokeless tobacco use among youth indicate that overall use of snus is low. The most popular smokeless tobacco brands identified by youth (12-17 years old) smokeless tobacco users continue to be the traditional moist snuff brands,[92] some of which make pouch products, but those are vastly different from snus products.

Preliminary data indicate that smokeless tobacco use could be associated with future smoking for youth and young adults. One small study found an association between snus use among non-smoking youth and young adults and increased likelihood of cigarette smoking initiation, current cigarette smoking, and more intense cigarette smoking two years later.[93] Though the proportions from the study are small, those findings are supported by older studies linking smokeless tobacco use to later cigarette smoking.[94] More recently, a study using data from the Population Assessment of Tobacco and Health (PATH) study found that non-smoking youth (12-17 years old) using smokeless tobacco (including snus) at baseline had higher odds of cigarette smoking initiation and two times the odds of past 30-day cigarette smoking at follow-up a year later compared to non-users.[95] This pattern is not isolated to the U.S.: a study from Norway found that age may be a factor in transitioning from snus to cigarettes. It found that people who started using snus before 16 years old were much more likely to become adult smokers compared to those who started snus later.[96] Moreover, initial smokeless tobacco use is also associated with later multiple tobacco product use. A survey of adolescents and young adults who had ever used tobacco found that those who initiated any tobacco use with smokeless

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92 U.S. Department of Health and Human Services (HHS), SAMHSA Center for Behavioral Health Statistics and Quality, *National Survey on Drug Use and Health*, 2014. ICPSR36361-v1, Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], 2016-03-22, http://doi.org/10.3886/ICPSR36361.v1.

93 Soneji, S, et al., "Associations Between Initial Water Pipe Tobacco Smoking and Snus Use and Subsequent Cigarette Smoking Results from a Longitudinal Study of US Adolescents and Young Adults," *JAMA Pediatrics* 169(2):129-136, 2015.

94 Tomar, SL, et al., "Is Smokeless Tobacco Use an Appropriate Public Health Strategy for Reducing Societal Harm?," *International Journal of Environmental Research and Public Health* 6:10-24, 2009, at 16. Severson, H, et al., "Use of smokeless tobacco is a risk factor for cigarette smoking," *Nicotine and Tobacco Research* 9(12):1331-1337, December 2007. Haddock, CK, et al., "Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males," *Preventive Medicine* 32:262-267, 2001. Tomar, S, "Snuff Use and Smoking in U.S. Men: Implications for Harm Reduction," *American Journal of Preventive Medicine* 23(3):143-149, October 2002. Tomar, S, "Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. experience," *Nicotine & Tobacco Research* 5(4):561-569, August 2003, http://www.ncbi.nlm.nih.gov/pubmed/12959794. See also, Tomar, SL, "Smokeless tobacco use is a significant predictor of smoking when appropriately modeled," *Nicotine & Tobacco Research* 5(4):571-573, August 2003, http://www.ncbi.nlm.nih.gov/pubmed/12959795.

95 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 Pediatrics* 172(2):181-187, 2018.

96 Lund, I & Scheffels, J, "Smoking and Snus Use Onset: Exploring the Influence of Snus Debut Age on the Risk for Smoking Uptake With Cross-Sectional Survey Data," *Nicotine & Tobacco Research* 16(6):815-819, 2014.

tobacco (or any other non-combustible product) had higher odds of using multiple tobacco products than those who initiated with a combustible product.[97]

Because most of the studies linking initial smokeless tobacco use to later smoking are older, TPSAC needs to determine how relevant these older findings are for Camel Snus, especially in the context of a tobacco product marketplace including e-cigarettes, which is currently more popular than even cigarettes.

CONCLUSION

These comments focus on issues that TPSAC should consider in evaluating R.J. Reynolds' modified risk tobacco product applications for its Camel snus products. First and foremost, FDA should finalize its proposed rule to limit the of N-nitrosonornicotine (NNN) level in all smokeless tobacco products, because that rule would inevitably affect the outcome of this application. In its applications, Reynolds relies heavily on data from Sweden, but from the limited data available, we have shown that not only do Swedish snus products differ from Camel snus in terms of toxicant exposure and possibly health risks, but also in the way that the products are used by consumers in each of the respective countries. Product regulation and marketing, which have a significant effect on the way products are perceived and used, also vary between the countries. These differences, along with available data on smokeless tobacco use and snus use in the United States, should be considered by TPSAC in its deliberations about the applications. Further, TPSAC should require Reynolds to submit data on adolescent risk perception of the proposed modified risk messaging to allow FDA to assess the potential for initiation of Camel snus or other smokeless tobacco products among youth and non-tobacco users as a result of using the proposed messaging.

Respectfully submitted,

Campaign for Tobacco-Free Kids

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[97] Soneji, S, Sargent, J, & Tanski, S, "Multiple tobacco product use among US adolescents and young adults," *Tobacco Control*, 2014, [Epub ahead of print], http://www.ncbi.nlm.nih.gov/pubmed/25361744.