

ADVISORY COMMITTEE BRIEFING MATERIALS:

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**ALCS on behalf of U.S. Smokeless Tobacco Company LLC
Briefing Materials
for
Copenhagen[®] Snuff Fine Cut Proposed Modified Risk Claim
January 2019**

Prepared by Altria Client Services LLC (ALCS) on behalf of
U.S. Smokeless Tobacco Company LLC
for the February 6-7, 2019
Tobacco Products Scientific Advisory Committee Meeting

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE
BRIEFING MATERIALS

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I. OVERVIEW

Altria Client Services LLC (“ALCS”) on behalf of U.S. Smokeless Tobacco Company LLC (“USSTC”)¹ submitted a Modified Risk Tobacco Product Application (MRTPA) on March 20, 2018 (STN MR0000108) to market Copenhagen[®] Snuff Fine Cut (Copenhagen[®] Snuff) with the following proposed modified risk claim:

“IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer.”

Copenhagen[®] Snuff is a moist smokeless tobacco (MST) product that has been on the market in the United States since 1822. It is not a new tobacco product as defined by Federal Food, Drug and Cosmetic Act (FD&C Act) Section 910(a)(1) and does not require premarket review and authorization.²

We seek a risk modification order under Section 911(g)(1) of the FD&C Act, which requires FDA to authorize a proposed modified risk claim when a 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 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 determining whether this standard is met, FDA evaluates whether the MRTPA adequately addresses the following questions:³

1. Is there adequate scientific substantiation of the proposed modified risk information?
2. What are the health risks of the MRTPA to individual tobacco users?
3. How do consumers perceive and understand the modified risk information?
4. What are the potential benefits and harms to the health of the population as a whole?

Questions 1 and 2 relate to Part A and questions 3 and 4 relate to Part B of Section 911(g)(1) of the FD&C Act. USSTC’s MRTPA adequately addresses all four questions. Therefore, the Tobacco Products Scientific Advisory Committee (TPSAC) should support FDA authorization of the proposed modified risk claim for Copenhagen[®] Snuff.

Copenhagen[®] Snuff, like similar MST products, presents both a dilemma and an opportunity.

¹ USSTC is a wholly owned subsidiary of Altria Group, Inc. (“Altria”). Altria Client Services LLC provides certain services, including regulatory affairs, research and development, and health sciences to the Altria family of companies. “We” or similar pronouns are used throughout to refer to USSTC.

² Copenhagen[®] Snuff subject to the MRTPA is the product for which FDA granted grandfathered status (Grandfather Number – GF1200194) on November 1, 2012.

³ FDA presentation by Benjamin Apelberg, PhD, MHS, Director, Division of Population Health Science, Office of Science, Center for Tobacco Products, U.S. FDA (October 23, 2018) “Tobacco Product Application Review: Modified Risk Tobacco Product Applications (MRTPAs)”

The dilemma arises from three indisputable facts:

- First, Copenhagen[®] Snuff and other smokeless tobacco (ST) products are not risk free, they are much lower risk than cigarettes, not only for lung cancer but for other tobacco-related diseases. This is the overwhelming consensus of the scientific, medical and public health communities. (Hatsukami et al., 2007; Zeller & Hatsukami, 2009). It is a scientific fact.
- Second, adult tobacco consumers (ATCs) have preexisting and deeply rooted misperceptions about the relative health risks of smokeless tobacco products compared to cigarettes. Our research, FDA's research, and more than a dozen published studies establish unequivocally that many ATCs erroneously believe that Copenhagen[®] Snuff and other ST products are equally harmful to cigarettes or even more harmful. More than 90% of adult smokers in FDA's Population Assessment of Tobacco and Health (PATH) survey state that ST products are just as harmful as or even more harmful than cigarettes.
- Third, the evidence from PATH shows that over half of adult smokers (more than 22 million) would consider using a tobacco product if they believed it offered a reduced risk of harm. If they had accurate information, some might quit smoking and convert completely to ST products, including many of the about 2.3 million who currently use both cigarettes and ST.

This dilemma gives rise to the opportunity: To give adult smokers a reason to make the transition from cigarettes to MST by providing them with accurate, non-misleading information, based on compelling scientific evidence, about the relative disease risks of these products. For smokers concerned with the health risks of smoking, the best thing to do is to quit all tobacco products. However, acknowledging the health risks of tobacco products and informing adult smokers about reduced harm products can complement, not compete with, proven prevention and cessation strategies.

The science and evidence summarized in these briefing materials demonstrate that:

1. Copenhagen[®] Snuff is significantly less harmful than cigarettes and switching completely from cigarettes to Copenhagen[®] Snuff reduces the risk of lung cancer;
2. The claim is truthful, accurate and substantiated by unequivocal scientific evidence, including the most current epidemiology data;
3. The claim is not misleading: tobacco users and nonusers understand that Copenhagen[®] Snuff poses health risks, and the claim does not diminish their perceptions of either its overall harmfulness or its risks for other diseases and conditions, such as mouth cancer, heart disease and nicotine addiction;

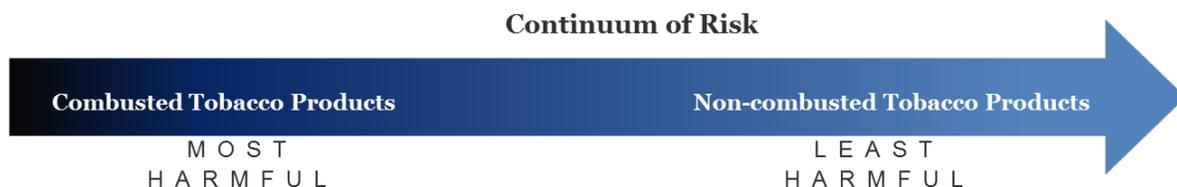
4. Adult smokers not planning to quit, particularly adult male smokers, are more likely to use this product and dual users are another logical audience; and
5. Even with a single exposure to the proposed modified risk claim, we estimate a modest reduction in overall mortality over a prediction period of 60 years if Copenhagen[®] Snuff is marketed with this claim.

a. Copenhagen[®] Snuff presents lower lung cancer risk and overall health risk for smokers who completely switch.

Copenhagen[®] Snuff is a non-combustible tobacco product, low on the continuum of risk. As the FDA has repeatedly acknowledged, there is a continuum of risk among tobacco products, with conventional, combustible cigarettes at the highest end of that spectrum and non-combustible products on the lower end.⁴

Figure 1: Continuum of Risk

"[W]e must acknowledge that there's a continuum of risk for nicotine delivery. That continuum ranges from combustible cigarettes at one end, to medicinal nicotine products at the other."
"[W]e must also take a new and fresh look at the noncombustible side."
Dr. Scott Gottlieb
FDA Commissioner



Among tobacco products, cigarettes result in the most morbidity and mortality. Smoking is the leading preventable cause of death in the U.S., primarily due to lung cancer, respiratory disease and cardiovascular disease. Non-combustible products, by contrast, are far less risky than cigarettes. A vast body of epidemiology on ST products (including Copenhagen[®] Snuff and similar MST products) demonstrates that such products present significantly lower harm than cigarettes.

Many global public health organizations accept the scientific fact that ST is far less hazardous than cigarette smoking. For example:

⁴ July 28, 2017 – “Protecting American Families: Comprehensive Approach to Nicotine and Tobacco.” Scott Gottlieb, M.D., Commissioner, White Oak Campus, Silver Spring, MD

“[T]he consumption of non-combustible tobacco is of the order of 10-1,000 times less hazardous than smoking, depending on the product.”⁵

“[U]sers of smokeless tobacco products generally have lower risks for tobacco-related morbidity and mortality than users of combustible tobacco products such as cigarettes.”⁶

“Overall therefore, in relation to the risks of the above major smoking-related diseases, and with the exception of use in pregnancy, [smokeless tobacco products] are clearly less hazardous, and in relation to respiratory and cardiovascular disease substantially less hazardous, than cigarette smoking.”⁷

“Studies have consistently reported that cigarette smoking significantly increases the risk of LC [lung cancer]. Most studies reported that ST users do not have an increased risk of LC compared with non-smokers.”⁸

Similarly, in the *Strategic Dialogue*, Zeller, et al., reached the following consensus in 2009:

“Cigarette smoking is undoubtedly a more hazardous nicotine delivery system than various forms of non-combustible tobacco products for those who continue to use tobacco, which in turn are more hazardous than pharmaceutical nicotine products.”⁹

“On the continuum of risk, non-combustible tobacco products are more likely to reduce harm than a smoked form of tobacco for individuals who would otherwise be using conventional cigarettes.”¹⁰

Based on our review of published epidemiology and our analyses of two large, nationally representative data sets from the National Center for Health Statistics -- specifically, data from the National Longitudinal Mortality Study (U.S. Census Bureau) (NLMS) and the National Health Interview Survey (CDC) (NHIS) -- we demonstrate that completely switching from cigarettes to ST products, like Copenhagen[®] Snuff, presents lower risk of lung cancer and that ST products present lower overall health risks than cigarettes.

⁵ Tobacco Advisory Group, Royal College of Physicians of London, *Protecting Smokers, Saving Lives* (London RCP 2002).

⁶ WHO Study Group on Tobacco Product Regulation (TobReg), *The Scientific Basis of Tobacco Product Regulation*, 951 WHO Technical Reports Series (2008).

⁷ European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), *Health Effects of Smokeless Tobacco Products* 115 (2008).

⁸ The Life Sciences Research Office, Inc. (LSRO) convened an Expert Panel of scientists and physicians in 2009 to conduct an independent, comprehensive scientific literature evaluation comparing the risks of ST product use to smoking cigarettes, to identify the critical characteristics that contribute to an evaluation of risk, and to determine whether there is sufficient evidence to categorize ST products according to risk. The project was funded by Philip Morris USA. The Differentiating Tobacco Risks (DTR) project is a case study of LSRO's Reduced Risk Review Project (RRRP), and utilized the risk assessment framework developed from the RRRP.

http://www.lsro.org/articles/dtr_0209.html

⁹ M. Zeller et al., *supra* note (Zeller & Hatsukami, 2009).

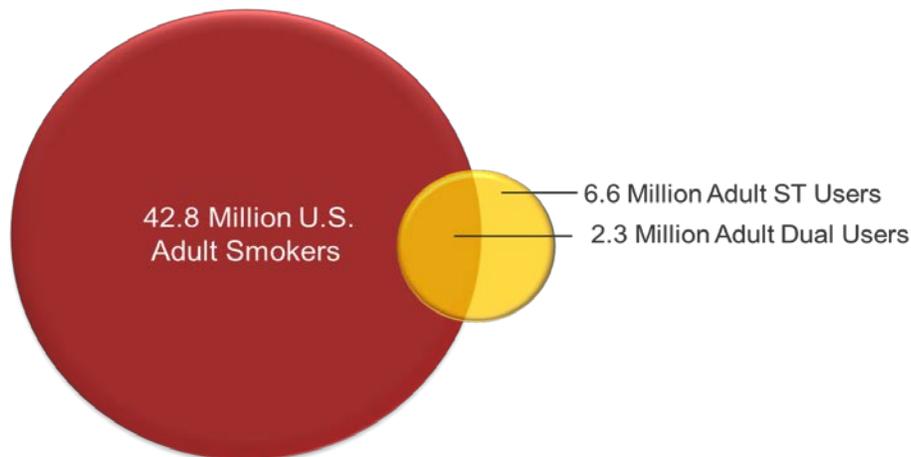
¹⁰ *Id.* at 327.

Copenhagen[®] Snuff has been marketed in the U.S. for many decades and accounted for a substantial market share during the time period when the epidemiological data were gathered. The existing epidemiological evidence can, therefore, be applied to assess the health risk of Copenhagen[®] Snuff and to establish that complete switching to Copenhagen[®] Snuff from smoking will similarly result in a lower risk of lung cancer.

b. Authorization of the modified risk claim for Copenhagen[®] Snuff will result in a net benefit to the population as a whole.

Adult smokers who will continue using tobacco products should be encouraged to switch to a less harmful product, like Copenhagen[®] Snuff. Notwithstanding efforts by government, public health and others to encourage them to quit, millions of adults are likely to continue using tobacco products, including a considerable number of adult ST consumers (~2.3 million) who continue to smoke. Such dual users¹¹ present a logical harm reduction opportunity because, having already made the choice to use ST, they may be more open to using ST exclusively and giving up cigarettes entirely.

Figure 2: Distribution of Adult Tobacco Consumers in 2014



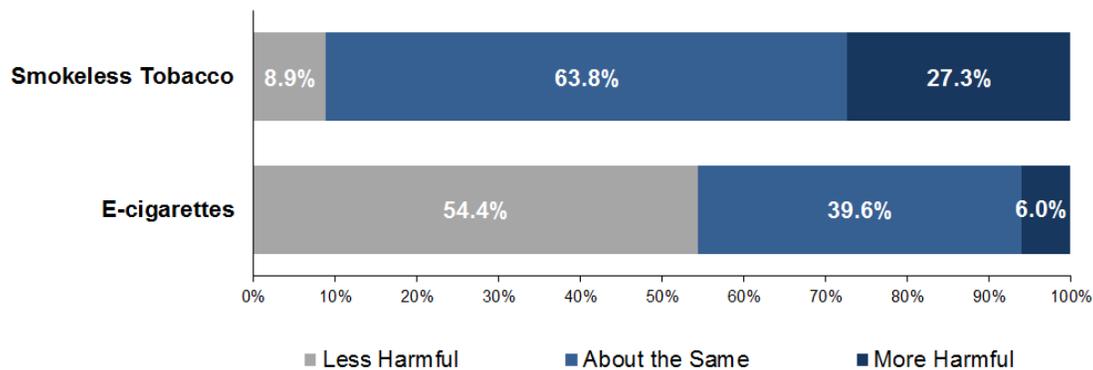
Source: Based on ALCS analysis of PATH Wave 1 data Sep 12, 2013 – Dec 14, 2014

Definitions: Cigarette smokers include those who report having smoked at least 100 cigarettes in their lifetime and now smoke every day or some days. Smokeless Tobacco (ST) users include those who report having used ST at least 20 times in their lifetime and now using ST every day or some days. Dual users include those who meet the following two conditions: (a) having smoked at least 100 cigarettes in their lifetime and were smoking every day or some days at the time of assessment; and (b) having used ST at least 20 times in their lifetime and were using ST every day or some days at the time of assessment.

¹¹ We refer to the population of ST consumers that also smokes cigarettes as “Dual Users.” This population is heterogeneous and we do not differentiate between levels of dual usage, which may consist of regular smokers that occasionally use ST or regular ST users that smoke cigarettes occasionally.

Many ATCs wrongly believe that ST products are as harmful as cigarettes or even more harmful. Substantial evidence exists that ATCs have deeply rooted misperceptions about the relative health risks of ST products compared to cigarettes. Our research, FDA’s research, and more than a dozen published studies establish unequivocally that many adult smokers have misperceptions regarding ST products. For example, in the PATH (Population Assessment of Tobacco and Health) WAVE 1 survey, the vast majority of adult cigarette smokers (more than 90%) erroneously believe that Copenhagen® Snuff and other ST products are equally harmful as cigarettes or even more harmful than cigarettes.¹² Figure 3.

Figure 3: Harm Perceptions Among Adult Cigarette Smokers

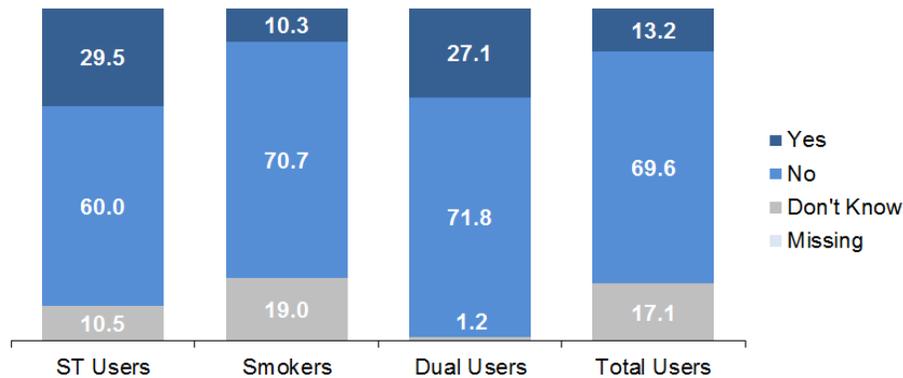


Source: ALCS Analysis of PATH Wave 1 (Sept ‘13- Dec ‘14) Adult Public Use File.

Similar findings are evident in the HINTS (Health Information National Trends) survey (Figure 4) where a vast majority of smokers (71%) and dual users (72%) did not believe that ST is less harmful than cigarettes.

¹² Source: ALCS Analysis of PATH Wave 1 (Sept ‘13- Dec ‘14) Adult Public Use File. In PATH, “Don’t Know” is not included in the valid response set. ST defined as loose snus, moist snuff, dip, spit, or chewing tobacco.

Figure 4: Proportion of Adult Tobacco Consumers that Believe ST is Less Harmful than Cigarettes



Source: Data from ALCS analysis of the 2015 National Cancer Institute Health Information National Trends Survey (HINTS). Proportions represent responses to the question: “In your opinion, do you think that some smokeless products, such as chewing tobacco, snus and snuff, are less harmful to a person’s health than cigarettes?”

‘ST users’ include individuals who had used smokeless tobacco (ST) at least 20 times and were using every day or some days at the time of the assessment but did not smoke cigarettes at the time of the assessment (n=60).

‘Smokers’ include individuals who had smoked at least 100 cigarettes and were smoking cigarettes every day or some days at the time of the assessment, but did not use ST at the time of the assessment (n=467).

‘Dual users’ include those who met lifetime criteria for both ST and cigarettes and were using both products every day or some days at the time of the assessment (n=21). ST included chewing tobacco, snus, snuff, or dip.

Published studies confirm the results of our analyses of PATH and HINTS data. In a 2005 survey of more than 2,000 adult U.S. smokers, only 10.7% correctly agreed that ST products are less hazardous than cigarettes, while 82.9% disagreed and 6.4% did not know (O’Connor, Hyland, Giovino, Fong, & Cummings, 2005). As noted by the authors:

“Here, smokers are *misinformed* in the opposite direction. Epidemiologic data suggests that [smokeless tobacco products] sold in the United States are significantly less dangerous than cigarettes In short, this U.S. national sample of adult smokers holds beliefs about the relative harm reduction potential of modified cigarettes and [smokeless tobacco products] that are *contrary to the available scientific evidence*. ”¹³

Table 1 depicts results from more than a dozen studies published between 2004 and 2013 on misperceptions of the relative risk of smokeless tobacco products compared to cigarette smoking.

¹³ *Id.* (emphasis added). Another study, published in 2007, examined adult smokers’ beliefs in the United States, Canada, and the United Kingdom and found that among the four, “U.S. smokers were least likely to believe that smokeless tobacco is less harmful, even though it is an available option for them.” R. J. O’Connor, *et al.*, *Smokers Beliefs about the Relative Safety of Other Tobacco Products: Findings from the ITC Collaboration*, 9 NICOTINE & TOBACCO RES. 1033, 1037, 1039 (2007).

Table 1: Perceived Harm and Risk Misperceptions

Authors (Date)	Findings Related to Risk Perceptions of ST	Percent Risk Misperception¹
Haddock et al. (2004)	Evaluated perceived risk reduction by switching to smokeless. 75% reported “no risk reduction” and only 2% reported “large risk reduction.” Authors found increased smoking cessation among those who perceived risk reduction for smokeless tobacco (ST).	75%
O’Connor et al. (2005)	Among smokers (aware of ST) 10.7% agreed, 82.9% disagreed, 6.4 % responded that they “did not know” in relation to the belief that ST products are less harmful than smoking.	83%
Smith et al. (2007)	Study examined perceived harm of smokeless products and cigarettes and found that 89.3% perceived dip /chew to be “as harmful” or “more harmful” than cigarettes.	89%
Tomar & Hatsukami (2007)	Among HS seniors, 58.7% perceived ST to have equal or greater risk of harm than cigarettes.	59%
O’Connor et al. (2007)	Across all Waves/Countries, 13% adult smokers agreed that there any ST products are less harmful than cigarettes. At Wave 3 among AS, 7.6% in the U.S., 9.7% in Canada, 11.7% in U.K., and 11.7% in Australia agreed that any ST products are less harmful.	>87%
Peiper et al. (2010)	In a survey of faculty, greater than 80% perceived ST to be “high risk” and less than 4% perceived “low” risk. Relative to cigarette smoking 36% believed ST was riskier and 50% no difference in risk.	86%
Borland et al. (2011)	Perception that some ST are “a lot less harmful” ranged from less than 20% in the U.S. and Canada to 40% or less in the U.K. and Australia.	60-80%
Callery et al. (2011)	Among four products tested, 30-60% reported perceptions of “less harmful.” Of the six conditions tested, 15-38% reported that ST was “more harmful.”	40-70%
Capella et al. (2012)	This study examined relative risk perceptions of ST vs. cigarettes. The authors reported that pairing a Harm Reduction Statement with a warning led to mixed results.	Not reported
Choi et al. (2012)	Some participants thought smokeless products were just as harmful or more harmful.	Not reported
Sami et al. (2012)	In focus groups of smokers on perceptions of ST and harm reduction, some “perceived [ST] as more ‘unhealthy’ than cigarettes.”	Not reported
Wray et al. (2012)	In young adult focus groups on perceived risk, the authors reported “varying levels of risk.”	Not reported
Borland et al. (2012)	Correct perception of ST as “a lot less harmful” after fact sheet intervention was 27.1% in the US, 28.3% in Sweden, 35.8% in Australia and 53.3% in the UK.	78-93% (pre-intervention)
Biener et al. (2014)	In an online survey of tobacco control professionals, about 30% incorrectly answered that ST is more harmful than cigarettes; unclear how many believe ST and cigarettes are equally harmful.	>30% (pre intervention)

¹Misperception means belief that ST is equally or more harmful than cigarettes.

Taken together, these studies demonstrate that smokers substantially overestimate the risk of various forms of ST. A significant proportion of smokers believe ST and cigarettes are equally harmful, and many believe ST is more harmful than cigarettes. Even tobacco control professionals are misinformed, with approximately 30% asserting that ST is more harmful than cigarettes. With respect to lung cancer, the subject of the proposed claim, these beliefs are indisputably incorrect.

Providing adult smokers with accurate, non-misleading information about the relative lung cancer risk of Copenhagen® Snuff compared to cigarettes is an important first step to empower adult smokers to make informed decisions and persuade them to completely switch to ST. Our proposed modified risk claim focuses on reduced lung cancer risk and emphasizes the benefit of complete switching. We focus on reduction in risk of lung cancer because it is among the most serious and fatal diseases caused by smoking and because extensive and unequivocal scientific evidence supports the proposed claim.

Figure 5: Advertising with the Proposed Modified Risk Claim



Our consumer study shows that the proposed claim, presented in the context of product advertising (Figure 5), is understood and is not misleading. We also observe in this study that

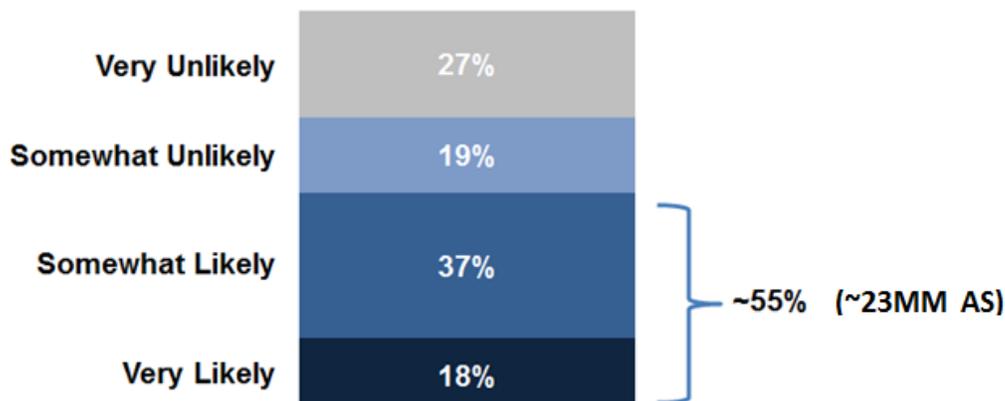
former and never tobacco users do not express intent to use Copenhagen[®] Snuff after reviewing the proposed modified risk claim.

Additionally, the results of our consumer study demonstrate a modest increase in the likelihood of use of Copenhagen[®] Snuff in current adult smokers not planning to quit. Using a model that integrates results from our consumer study and our epidemiologic analyses, we estimate a modest reduction in overall mortality (93,000 premature deaths avoided) in the U.S. population over a 60 year period if Copenhagen[®] Snuff is marketed with the proposed claim.

c. The proposed modified risk claim presents a harm reduction opportunity for adult smokers.

Tobacco harm reduction is more than a public health objective – it is a priority for many adult smokers. Recent PATH data demonstrates that many adult smokers (more than 22MM, 55%) are interested in and likely to use reduced-risk products marketed with a reduced risk claim (Figure 6).

Figure 6: Interest in Reduced-Risk Tobacco Products Among Established Smokers



Source: Based on ALCS analysis of PATH Wave 1 data Sep 12, 2013 – Dec 14, 2014; Response to question – “If a tobacco product made a claim that it was less harmful to health than other tobacco products, how likely would you be use that product?”

Copenhagen[®] Snuff, marketed with an FDA-authorized modified risk claim, will provide a reduced-risk alternative for adult smokers not planning to quit. Continued cigarette smoking, including sustained dual use, is not a desirable public health outcome. We focused on developing a modified risk claim that could help adult smokers better understand the relative risks of Copenhagen[®] Snuff and cigarettes and encourage them to switch completely to Copenhagen[®] Snuff. We verified this claim to be:

- relevant to adult smokers not planning to quit;

- clear and believable;
- understood and not misleading; and
- substantiated by robust scientific evidence.

II. **SCIENTIFIC SUBSTANTIATION OF THE PROPOSED MODIFIED RISK INFORMATION AND THE HEALTH RISKS TO THE INDIVIDUAL TOBACCO PRODUCT USERS**

Based on our review of published epidemiology and our analyses of NLMS and NHIS data, we demonstrate that:

- ST products have lower lung cancer risk than cigarettes.
- Switching to ST from cigarette smoking lowers lung cancer mortality risks compared to continued smoking.
- ST users have substantially lower mortality risks for all causes, malignant neoplasms (including lung cancer), and diseases of the heart than cigarette smokers.
- Although ST products are less harmful than smoking, they are not without risk and increase certain types of disease risks relative to no tobacco use.

We conclude that switching completely to Copenhagen® Snuff from cigarettes reduces the risk of lung cancer. The weight and consistency of the evidence substantiates our proposed claim.

a. The harm caused by tobacco use is primarily attributable to cigarette smoking.

The U.S. Surgeon General has described cigarette smoking as “the single greatest cause of avoidable morbidity and mortality in the United States” [Surgeon General Report (2004)]. According to the Centers for Disease Control and Prevention (CDC), “[s]moking is the primary causal factor for at least 30% of all cancer deaths, for nearly 80% of deaths from chronic obstructive pulmonary disease, and for early cardiovascular disease and deaths.” We agree with the overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema, and other serious diseases in smokers and is addictive. Smoking is directly responsible for more than 80% of lung cancer deaths [Surgeon General Report (2004)]. More people in the U.S. die from lung cancer than any other type of cancer. The five-year survival rate for new lung and bronchus cancer diagnoses in the U.S. (2007-2013) is 18.1%, according to SEER data from the National Cancer Institute.¹⁴

Quitting tobacco use is the most effective means of reducing the risk of tobacco-related disease. For those smokers who do not quit all tobacco, completely switching from cigarettes

¹⁴ National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program, Cancer Stat Facts: Lung and Bronchus Cancer, <https://seer.cancer.gov/statfacts/html/lungb.html> (accessed Jan. 7, 2018).

to demonstrably less hazardous ST products can reduce the risk of lung cancer and other serious diseases.

b. Epidemiological evidence on the health risks of ST applies to Copenhagen[®] Snuff.

Epidemiology studies rarely identify specific products used by the cohorts studied, which can limit the ability to apply epidemiological data directly to specific products. As explained below, however, existing epidemiology data for U.S. smokeless tobacco products is especially relevant to assess the health risks of Copenhagen[®] Snuff. Our reasoning, in brief, is as follows. First, MST products were the predominant form of ST¹⁵ used during the time period of the major U.S. epidemiology studies. Second, Copenhagen[®] Snuff and other USSTC MST products occupied a sizeable market share among the MST products used during the time period of these studies, which means that the epidemiological data reasonably reflects the health effects of Copenhagen[®] Snuff and other USSTC products. Third, the production process for USSTC MST products, including for Copenhagen[®] Snuff, was essentially unchanged over the time period of these studies, except for refinements, such as improved process control and reduced TSNA formation. These changes presumably did not increase, and arguably could decrease, the potential health risks of the product.

Simply put, this epidemiological evidence is directly applicable to support the granting of this MRTP claim.

¹⁵ The term "smokeless tobacco" comprises a variety of products demonstrating a range of design characteristics and usage patterns. The U.S. smokeless tobacco market has comprised several product forms, including moist snuff, dry snuff, loose leaf chewing tobacco, plug, and twist.

MST, which leads the U.S. market, generally consists of fire- and air-cured dark tobaccos which are cut into various lengths (i.e., fine and long cut) before undergoing a manufacturing process, which, in the case of USSTC, is a fermentation process. MST can be packaged and sold in either a loose or prepackaged format. The loose product allows the consumer to select the amount used (i.e., commonly called a pinch), while the prepackaged products contain a predefined amount wrapped in a sachet of paper material (i.e., commonly called pouches).

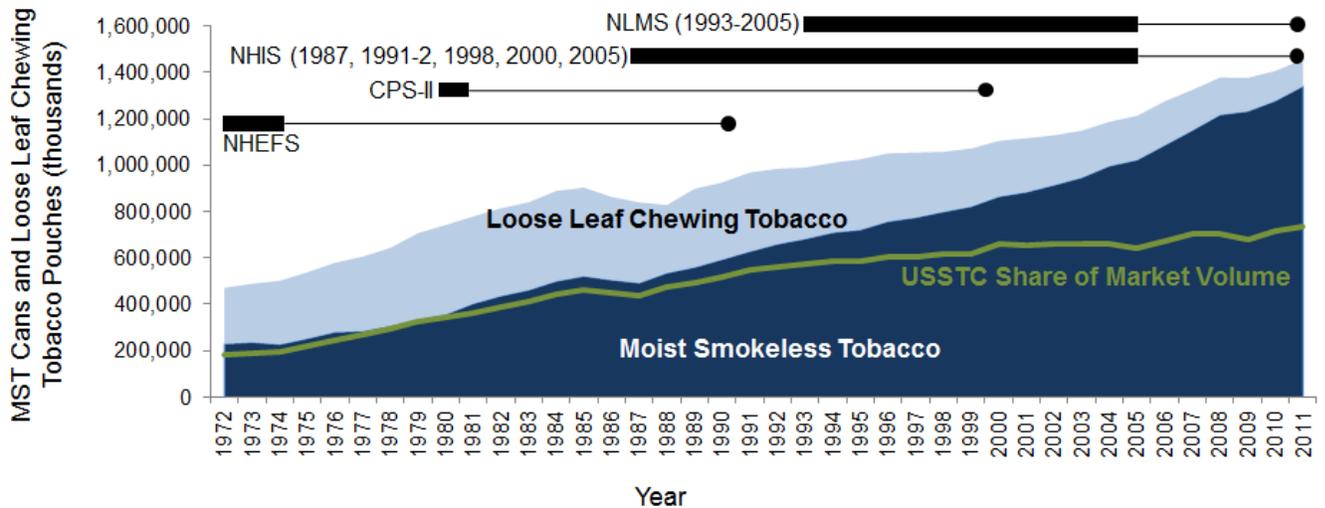
Loose-leaf chewing tobacco comprises shredded air-cured tobacco treated with flavoring and processing solutions to keep the tobacco moist and pliable. Dry snuff is manufactured by heat treating fire-cured tobaccos subsequently grinding the leaves into a fine powder. Dry snuff was typically inhaled through the nostril, but could also be used orally by rubbing the tobacco on the gum. Dry snuff products were popular among women in the southern U.S. many years ago and was the smokeless product type represented in the oral cancer epidemiology study conducted by Winn in 1981 (Winn et al., 1981). Dry snuff has never maintained a majority of the U.S. ST market and currently maintains only a small U.S. market share.

International smokeless product types and usage patterns are quite different from U.S. MST, and the health risk profiles vary widely. In some Southeast Asian countries smokeless tobacco is often combined with betel and areca for chewing (e.g., pan masala, gutka, Manipuri tobacco, mawa, and dohra). Other smokeless tobacco forms such *Maras powder* mixed with ash obtained from the oak, or Toombak, can be found in Turkey or Sudan. A high incidence of cancer (most notably oral cancer) has been associated with this practice, leading IARC¹⁵ to conclude that betel quid with tobacco, betel quid without tobacco, and areca nut are all carcinogenic to humans.

c. MST products were the predominant form of ST used during the time period of the major U.S. epidemiology studies.

MST products are the predominant form of ST use. Figure 7 shows the estimated unit volume of MST and loose leaf chewing tobacco between 1972 and 2011. In 1972, MST products already accounted for nearly half of the ST category. Since then, the market share of MST products has steadily grown, accounting for half the category by the early 1980s, and 75% by the late 1980s. MST’s rise to dominate the ST category coincides with the timing of major epidemiology studies of ST products conducted in the U.S., as shown by Figure 7. Collectively, these epidemiology studies span 1972 to 2011. Over the time period studied, therefore, the health effects of using smokeless tobacco products, as reported by U.S. epidemiological data, were increasingly associated with the use of MST.

Figure 7: USSTC Volume within MST and Chewing Tobacco Category (1972-2011) and Study Periods of Prospective Studies of the Health Effects of ST Products



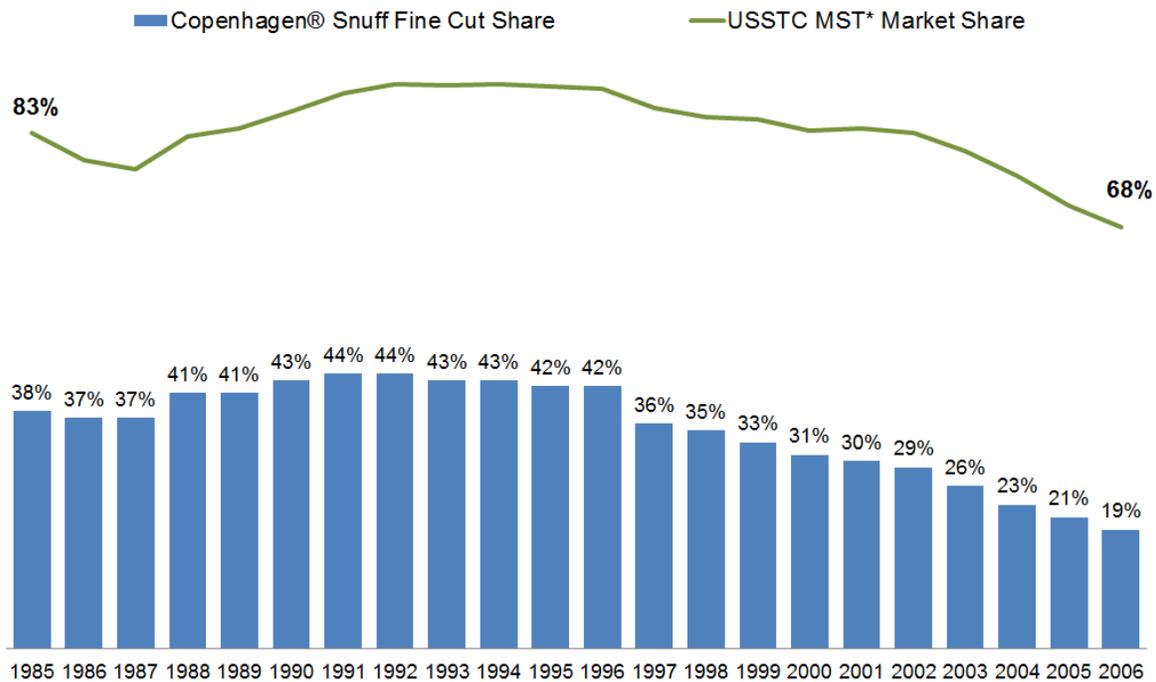
Source: Unit volume of moist smokeless tobacco and loose leaf chewing tobacco derived from Maxwell Reports 1972-2011 and study periods for prospective epidemiological studies of smokeless tobacco. USSTC volumes are based on USSTC historical shipment data and USSTC RAD SVT projected volume and share.

NLMS=National Longitudinal Mortality Study; NHIS=National Health Interview Survey; CPS-II=Cancer Prevention Study-II; NHEFS=NHANES I (National Health and Nutrition Examination Survey) Epidemiologic Follow-up Study. Black boxes represent the baseline periods for studies and black circles represent the end of follow-up period.

d. Copenhagen® Snuff and USSTC products occupied a sizeable market share among the MST products used during the time period of these studies.

Figure 8 provides market share data for USSTC products and Copenhagen® Snuff through 2006, which encompasses the latest survey periods of the relevant epidemiological evidence. In 1985, for example, USSTC products comprised 83% of MST industry volume, and Copenhagen® Snuff accounted for 38% of the MST category. Over the time period of the epidemiology studies, Copenhagen® Snuff occupied a sizeable market share among the MST products. For this reason, and the reasons presented above, we conclude that the health risks of Copenhagen® Snuff in particular can be sufficiently assessed using existing epidemiology data for U.S. smokeless tobacco products.

Figure 8: Contribution of Copenhagen® Snuff to USSTC’s Market Share, 1985-2016



Source: Copenhagen® Fine Cut Natural and USSTC Shipments 1985-2006 based on USSTC historical shipment data and USSTC RAD SVT projected volume and share. 1985-2000 share estimated using USSTC's growth rate during that period and total industry total volume as of 2002.

*Moist Smokeless Tobacco (MST). Yearly data shown until Feb. 2007 (grandfathered product date).

e. USSTC MST products, including Copenhagen[®] Snuff, have been consistently manufactured and process refinements over time have lowered TSNA levels.

From its earliest days, USSTC has sourced Dark Air-cured and Dark Fire-cured tobaccos for all of its MST products from growers in the same regions of Kentucky and Tennessee. USSTC has produced MST using a fermentation process for almost 200 years which can be documented based on historical product formulas for Copenhagen[®] Snuff to as early as 1905. In brief, this process includes addition of water, flavoring ingredients and salts, to a blend of dried, cut tobacco.

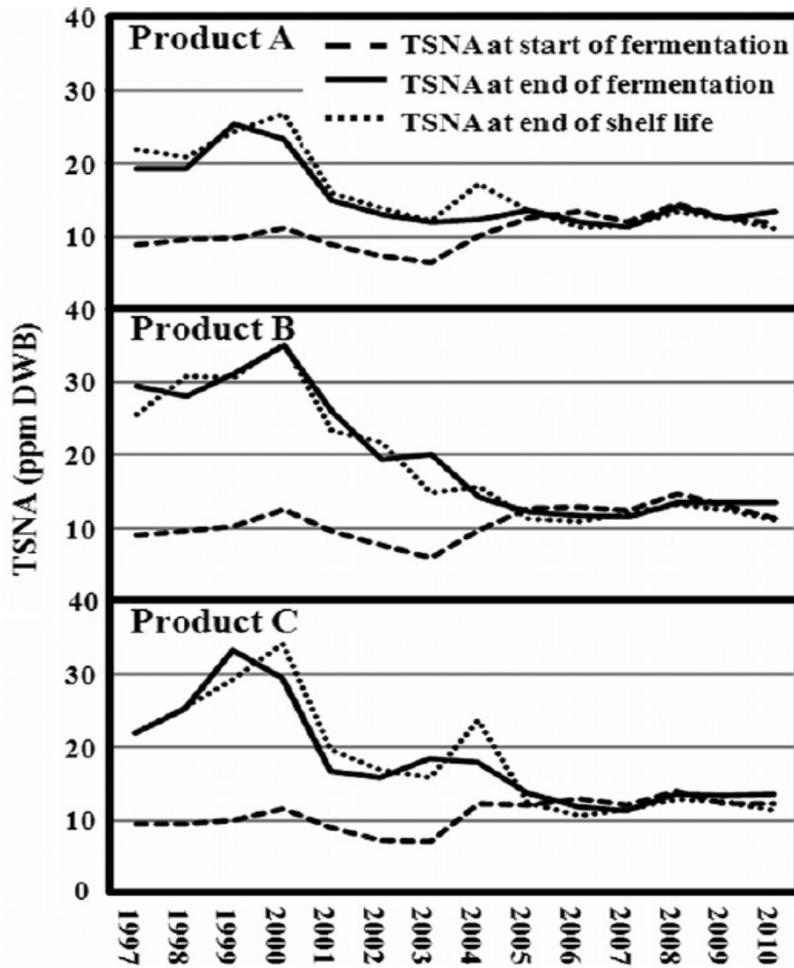
Across its product portfolio, USSTC MST products have contained the same tobacco types and have been manufactured using consistent processes over time, other than process improvements that lowered TSNA levels as described below. Copenhagen[®] Snuff, in particular, used tobacco types, blends, and manufacturing processes comparable to all USSTC MST products, throughout the time period of the epidemiology studies. Copenhagen[®] Snuff, therefore, has a similar constituent profile, and health risks reasonably expected to be similar, compared to other USSTC MST products.

Although USSTC's moist snuff production process has remained almost unchanged, there have been process refinements. USSTC implemented these refinements to improve process control and reduce TSNA formation in its current MST products, relative to historical levels (Fisher et al., 2012) as shown in [Figure 9](#). The refinements that resulted in substantial TSNA reductions of up to 90% in USSTC's products by the late 1990s included:

- improvements to farming practices – developing low converter seed varieties to help reduce TSNA formation in tobacco leaf relative to earlier generations of seed varieties.
- manufacturing process enhancements – implementing procedures in the manufacturing process more than a decade ago that prevent TSNA formation from the time USSTC purchases tobacco leaf from farmers through the end of retail shelf life of the product; and
- Vertically Integrated Process Management (VIPM) – using production equipment that can be easily sanitized and systematically examining TSNA levels.

These refinements to USSTC's moist snuff production process do not make existing epidemiology any less relevant to current USSTC moist snuff products, including Copenhagen[®] Snuff.

Figure 9: Average TSNA Levels (PPM, Dry Weight Basis) in Commercial Moist Smokeless Tobacco Products A, B, and C 1997–2010



Source: (Fisher et al., 2012). (Figure 7).

The heavy dashed lines indicate TSNA levels in tobacco blend prior to fermentation with annual average levels ranging between 5.9 and 13.5 ppm across the three brands. The solid lines indicate annual average TSNA levels at the end of fermentation. The light dashed lines indicate TSNA levels after storage simulated shelf-life conditions. After 2005, fermentation process control was such that TSNA were not formed during the process and, therefore, TSNA levels are determined by levels in starting material.

Product A = Copenhagen Fine Cut; Product B = Copenhagen Long Cut; Product C = Skoal Fine Cut

f. The totality of the health risk evidence supports the proposed modified risk claim for Copenhagen® Snuff.

We conclude from multiple lines of evidence that ST is less risky than cigarettes and switching completely to Copenhagen® Snuff from cigarettes reduces risk of lung cancer. Within the hierarchy of evidence, we assign significant weight to the epidemiological studies as they provide health outcomes resulting from long-term product use behavior under real-world conditions. Nonclinical and clinical studies provide additional information regarding the likelihood of health outcomes and the mechanistic basis for the epidemiological findings.

- Epidemiological evidence provides the best proof that use of ST products presents substantially lower morbidity and mortality risks compared to cigarette smoking, particularly lung cancer. Nonclinical and clinical evidence further supports this conclusion.
- ST is non-combustible. As a result, there is no tar or tobacco smoke and no direct pulmonary exposure to the thousands of harmful and potentially harmful constituents (HPHCs) found in tobacco smoke. Combustion related HPHCs are either absent or present at significantly lower levels in ST compared to cigarettes.
- The biological effect of ST is far lower than cigarettes, as demonstrated in a number of *in vitro* assays assessing perturbations in biological systems including cytotoxicity, cell proliferation, cell cycle control, apoptosis, and genotoxicity.
- Moreover, while some, animal studies, conducted under exaggerated exposure conditions that do not reflect human use level indicate perturbations in biological systems, the epidemiological evidence indicates that these changes are not relevant to human disease.
- Biomarkers of exposure to combustion-related HPHCs in ST users are similar to those observed in non-tobacco users and significantly lower than in cigarette smokers, confirming the product chemistry analyses observations.
- Favorable changes in biomarkers of potential harm related to chronic inflammation have been observed in ST users compared to smokers, further confirming that the reductions in exposure to many HPHCs likely relate to reduction in disease risk.

Our analysis of the health risks associated with Copenhagen® Snuff incorporates two sets of epidemiology data comprising the most current risks for U.S. marketed products. Specifically, we examine mortality associated with ST and cigarettes based on two large, nationally representative linked mortality datasets available through 2011. The National Center for Health Statistics (NCHS) has linked various surveys with death certificate records from the National Death Index (NDI). We analyzed the survey respondents from the National Health Interview Survey (NHIS) (1987, 1991, 1992, 1998, 2000 and 2005) and the National Longitudinal Mortality Survey (NLMS) administered from 1993 through 2005. Our NHIS analyses consisted of 154,391 total respondents, including 3,006 current ST users and the NLMS analyses comprised of 210,090 total respondents including 3,492 current ST users. Because of the longer follow-up period for the NHIS study, the number of deaths recorded for any specific disease is generally greater than that recorded in the NLMS data. Together, these surveys contain tobacco use and mortality data spanning the mid-1980s to 2011, and allow estimation of mortality risks which are likely more reflective of the hazards encountered by ST users in the U.S. population using the most currently available products, including MST.

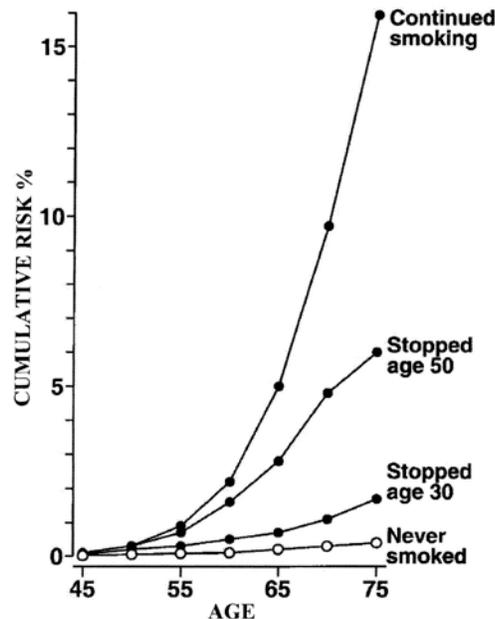
We estimate the mortality hazard ratio (HR) using a Cox Proportional Hazards Model for all-causes, malignant neoplasms (including respiratory - trachea, bronchus and lung, oral cavity, lip and pharynx, digestive organs, esophagus, pancreas, colon, rectum and anus and genitourinary system) and lung cancer (trachea, bronchus and lung).

We also examine published epidemiological evidence related to the use of ST. We summarize our conclusions based on three lines of evidence: lung cancer risk when switching completely to Copenhagen® Snuff from cigarettes, all-cause mortality of ST compared to cigarettes, and all cancer mortality risk of ST compared to cigarettes.

i. Switching to Copenhagen® Snuff from cigarettes reduces lung cancer risk.

Cigarette smoking has a high risk of lung cancer. The scientific evidence indisputably establishes that smoking cessation leads to significant reduction in health risks, including reduction in lung cancer risks, as indicated by Figure 10. The totality of the evidence, including our analyses and published literature, further demonstrates that smokers would reduce their lung cancer risk by switching completely to Copenhagen® Snuff.

Figure 10: Cumulative Risk of Lung Cancer Mortality Among Men According to the Age When They Stop Smoking



Source: (Vineis et al., 2004)

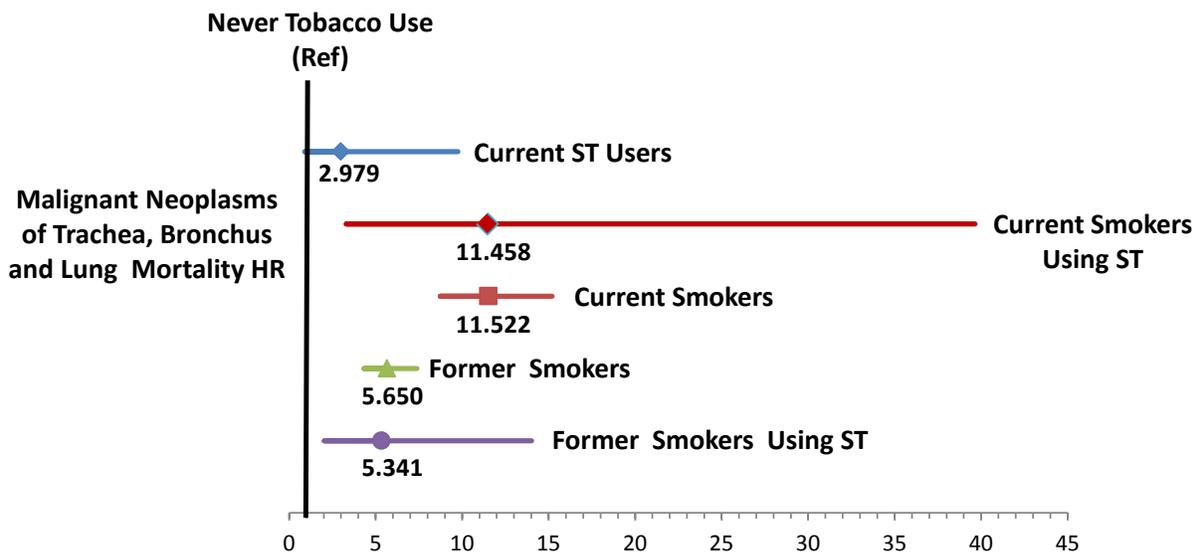
Our analyses of the NHIS and NLMS data confirm high lung cancer incidence in smokers, with lung cancer mortality risk estimates approaching a 12-fold increase over never use of tobacco. Lung cancer incidence and mortality remain strongly correlated, despite innovations in medical detection and treatment, due to the limited survival rate for lung cancer (18.1% five-year survival rate, according to recent SEER data).¹⁶

¹⁶ National Cancer Institute, Surveillance, Epidemiology, and End Results Program, Cancer Stat Facts: Lung and Bronchus Cancer, <https://seer.cancer.gov/statfacts/html/lungb.html> (accessed Jan. 7, 2018).

The lung cancer risk of using smokeless tobacco is much lower than smoking cigarettes. Both NHIS and NLMS datasets contained very few reports of deaths associated with lung cancer in exclusive ST users. These low incidences prevented calculation of a reliable estimate of lung cancer HR. Some published epidemiology studies report elevated lung cancer risks in ST users; nevertheless, these risks remain substantially lower than those observed for cigarette smokers.

The NLMS data provide a sufficient sample to calculate HR for neoplasms of the trachea, bronchus, and lung, and other respiratory diseases, as shown in Figure 11. Cigarette smokers had a mortality risk from neoplasms of the trachea, bronchus, and lung of over 10, while that risk is reduced by about 50% in former smokers. Although the risk estimate for lung cancer for former smokers who use ST is based on few deaths, resulting in wide confidence intervals around the point estimate, the trend is clear – using ST after quitting smoking is associated with lower lung cancer risk compared to continued smoking.

Figure 11: Mortality Hazard Ratios¹ from Neoplasms of the Trachea, Bronchus, and Lung: Adjusted Hazard Ratio Estimates for Various Tobacco Use Practices Compared to Never-Tobacco Users



¹ Estimates derived from Cox proportional hazards analysis of the NLMS datasets with covariate adjustments (gender, race [white, non-white], age, education, family income, self-reported health status, tobacco use, and cigarettes per day. The analysis was conducted on all respondents (P4 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters) (MRTPA, Section 7.4.1 Linked Mortality Analysis).

Published epidemiology studies report mixed outcomes of possible association between ST use and lung cancer. A meta-analysis of data specific to studies among the U.S. population suggested no association between ST use and lung cancer (Lee & Hamling, 2009). On the other hand, a recent study by Andreotti et al. (2016) provided lung cancer estimates using data from the Agricultural Health Study for ST users. Although the authors report increased

risk for lung cancer in ST users when compared to non-tobacco users, this risk is still lower than that observed for smokers, who had a lung cancer risk 15 times greater than non-tobacco users.

Even if one accepts the reported association between ST use and excess lung cancer mortality risk seen in some individual studies, this risk is far lower than that observed for cigarette smoking – the basis for our proposed claim.

Among other evidence, we substantiate our proposed modified risk claim that switching completely to Copenhagen[®] Snuff from cigarettes reduces risk of lung cancer as follows:

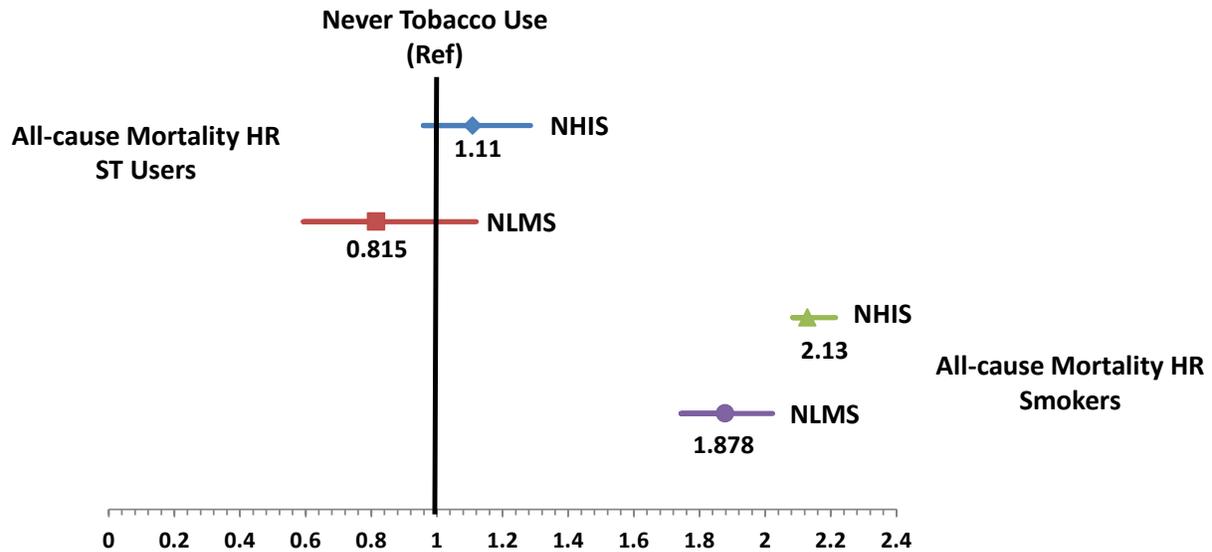
- First, cigarette smoking is the leading cause of lung cancer; however, public health authorities have not concluded that use of ST products *causes* lung cancer.
- Second, our analysis of the NLMS dataset indicates that dual users (current cigarette smokers who use ST) have similar lung cancer risk to exclusive cigarette smokers, providing further evidence that using ST does not add to the lung cancer risk of cigarette smoking.
- Third, our analysis of the NLMS dataset indicates that former cigarette smokers who use ST have similar lung cancer risk to former smokers who do not use tobacco products.

ii. ST use presents substantially lower all-cause mortality risk than cigarette smoking.

All-cause mortality is often an overall estimate of mortality from all diseases including lung cancer. [Figure 12](#) presents estimated all-cause mortality HR, derived from the NLMS and NHIS datasets, to compare the incidence of fatal diseases in ST users, cigarette smokers, and never-tobacco users. This analysis demonstrates that the use of ST products, including Copenhagen[®] Snuff, is not associated with significant increases in all-cause mortality risks compared with never using tobacco products. It further illustrates a substantial reduction in all-cause mortality for ST users compared to cigarette smokers. However, some published literature (Gupta, Gupta, Sharma, Sinha, & Mehrotra, 2018; Rostron et al., 2018; Timberlake, Nikitin, Johnson, & Altekruse, 2017) suggests a possible association between ST use and heart disease. Of note, our analysis showed substantially lower mortality risk for diseases of the heart in ST users as compared to cigarette smokers.

While this analysis shows no increase in *mortality* risk compared with never use, it does not show, and it is not intended to suggest, that ST use is without risk.

Figure 12: All-Cause Mortality Hazard Ratios¹ in ST Users and Smokers Compared to Never Users

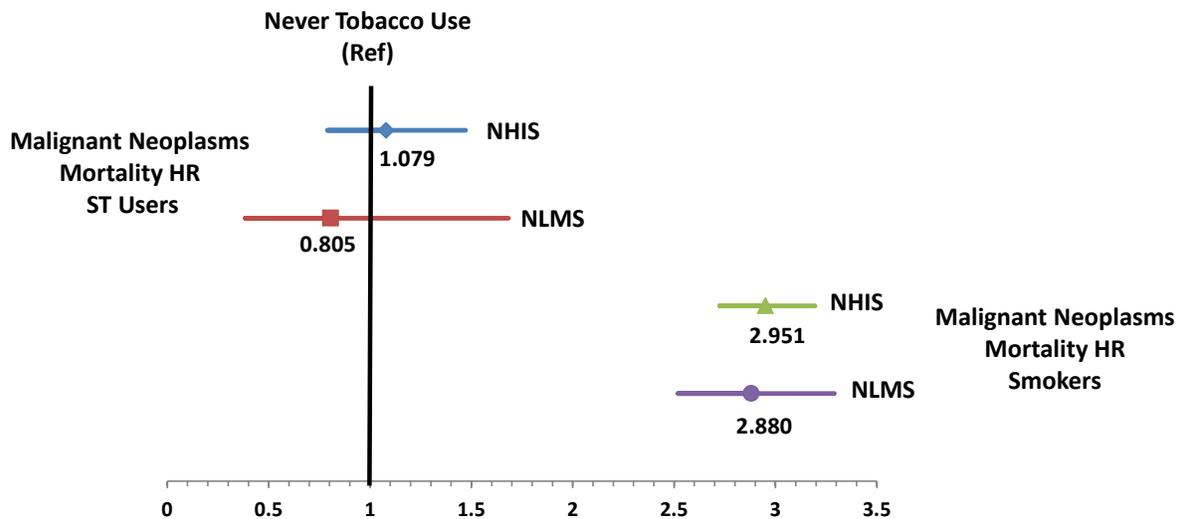


¹ Estimates derived from Cox proportional hazards analysis of the NLMS datasets with covariate adjustments (gender, race [white, non-white], age, education, family income, self-reported health status, tobacco use, and cigarettes per day. The analysis was conducted on all respondents (P4 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).

iii. ST use presents substantially lower mortality risks for all cancers than cigarette smoking.

Malignant neoplasms are a subset of all-cause mortality, known to be associated with cigarette smoking, and reported in literature to be associated with ST use. Figure 13 shows the estimated mortality HR from malignant neoplasms (all types) from the NHIS and NLMS datasets for ST users and cigarette smokers compared to never tobacco use. ST users do not have increased mortality risks from malignant neoplasms compared to never tobacco users. In contrast, cigarette smokers have significantly elevated mortality risks, due to malignant neoplasms, compared to never tobacco users and ST users.

Figure 13: Mortality Hazard Ratios¹ from Malignant Neoplasms in ST Users and Smokers Compared to Never Users



¹ Estimates derived from Cox proportional hazards analysis of the NLMS datasets with covariate adjustments (gender, race [white, non-white], age, education, family income, self-reported health status, tobacco use, and cigarettes per day. The analysis was conducted on all respondents (P4 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).

g. Conclusions – Scientific Substantiation of the Proposed Modified Risk Claim and the Health Risk to the Individual Tobacco User

Based principally on our analysis of well conducted, public, nationally representative datasets – NHIS and NLMS, as well as our evaluation of published epidemiological studies and analysis of additional lines of evidence, we conclude:

- ST is non-combustible and, therefore, presents no direct pulmonary exposure to HPHCs. Combustion related HPHCs are either absent or present at significantly lower levels in ST compared to cigarettes. Human studies with ST use confirm reductions in biomarkers of exposure to many constituents and favorable changes in biomarkers of chronic inflammation.
- Switching completely to Copenhagen® Snuff significantly reduces mortality risk compared to cigarette smoking, particularly for lung cancer and all-cause mortality.
- Specific to lung cancer, information in the NLMS and NHIS datasets is consistent with previous published investigations of mortality risk in ST users and adult smokers, showing substantially greater risk for mortality from lung cancer in smokers compared to exclusive ST users.
- While not risk free, Copenhagen® Snuff presents significantly lower disease risks compared to cigarettes. Our analysis of the NLMS and NHIS datasets finds that mortality from malignant neoplasms is substantially lower among ST users than among adult smokers. This holds true even for diseases that public health authorities

have causally associated with ST use, including oral, esophageal, and pancreatic cancers. (MRTPA, Section 6.1, Table 6.1-10).

These conclusions scientifically substantiate the proposed claim that switching completely from cigarettes to Copenhagen® Snuff reduces risk of lung cancer.

III. CONSUMER PERCEPTIONS AND UNDERSTANDING OF THE MODIFIED RISK CLAIM

ALCS designed a perception and behavior program to develop and test modified risk claims for comprehension and risk perceptions. We developed the proposed modified risk claim language to be clear, relevant, believable and easily understandable.

a. Claims Language Development and Assessment

We first developed consumer-centric, modified risk claims language, supported by the scientific evidence, based on careful review of the published epidemiology and our analysis of the linked mortality datasets. During the claims language development phase, ALCS conducted two claims qualitative studies (for development and assessment of the language) to determine claims language combinations that ATCs would find clear, understandable, relevant, and believable. In the first qualitative study,¹⁷ we learned that claims language must follow some general principles in order to be credible:

- The message must be strong, but language should not be so strong that it is unbelievable.
- The message needs to be congruent with what people already believe to be true about the health risks of ST products (e.g., the claims should not conflict with the warning statements).
- The message cannot be alienating (e.g., referring to “*exclusive* use of this product” was alienating to consumers; whereas, “switching completely” was considered strong without being overly alienating).
- The message must be easy to understand (e.g., the terms “COPD” and “emphysema” were not well understood by some participants).

The second qualitative study¹⁸ resulted in the following findings as part of the claims development process:

- Although participants disliked introductory claim language such as “switching completely” and “exclusive use,” these messages were understood to mean 100%

¹⁷ The study consisted of five focus groups of adult male smokers who did not reject MST and dual users of MST and cigarettes (n = 63).

¹⁸ The study consisted of one-on-one interviews (n = 22) among adult male smokers who did not reject MST (i.e., those saying they are “neutral,” “somewhat willing,” or “very willing” to try MST at some point in the future) and dual users of cigarettes and MST.

replacement of cigarettes with MST; whereas terms like “as an alternative” or “use instead of” were not interpreted to mean 100% replacement.

- Only a few participants said that the claim message developed during the research would positively affect their intent to use MST.
- Fewer than half of the participants said that the claim might affect their perceived risk to health from using MST.
- The majority of participants questioned the credibility and/or believability of various claim statements (e.g., general health), saying that a given claim statement could contradict the warning statement, while others saw claim statements (e.g., mouth cancer) as a tradeoff between health risks associated with MST and cigarette smoking.

Importantly, across the claims development qualitative studies, while only a few participants stated positive changes in intention to use MST, they were typically dual users. Additionally, while participants viewed multiple claim statements throughout the interview, the research involved only a single exposure occasion.

The results of the claims qualitative studies further suggest that individuals’ beliefs about the risk of ST are likely to influence their interpretation of potential claim language. As referenced by Slovic (1987), “New evidence appears reliable and informative if it is consistent with one’s initial beliefs; contrary evidence tends to be dismissed as unreliable, erroneous, or unrepresentative.”¹⁹

Additionally, some adult smokers believe the risks to health from cigarettes and MST are equivalent. However, when evaluating a specific risk tradeoff, social or ideological concerns come into consideration. For example, during our claims development research, the visible aspects of contracting mouth cancer through ST made this risk a stronger negative than the risk of lung cancer.

While understanding that there may be positive rationale for the inclusion of other claims, we selected the claims language based on:

- its relevance and understanding to the individual smoker;
- its level of clarity and believability relative to other claims tested; and
- robust scientific evidence substantiating the proposed modified risk claim.

b. Modified Risk Claim Testing

Through our modified risk claims development, we selected the following proposed modified risk claim:

“IF YOU SMOKE CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer.”

¹⁹ R. Nisbett and L. Ross. *Human Inference: Strategies and Shortcomings of Social Judgment*. Prentice-Hall, Englewood Cliffs, NJ (1980).

Through our research, we concluded that this claim, when presented in the context of advertising (e.g., including warnings and product imagery):

- conveys accurate information, supported by the scientific evidence;
- is understandable and relevant to ATC; and
- would not lead consumers to believe that Copenhagen[®] Snuff is without risk.

While this claim met the criteria for testing phase inclusion, many participants still associated ST products to be as risky as cigarettes due to other perceived negative implications to total health and specific diseases (e.g., mouth cancer).

Also, of note:

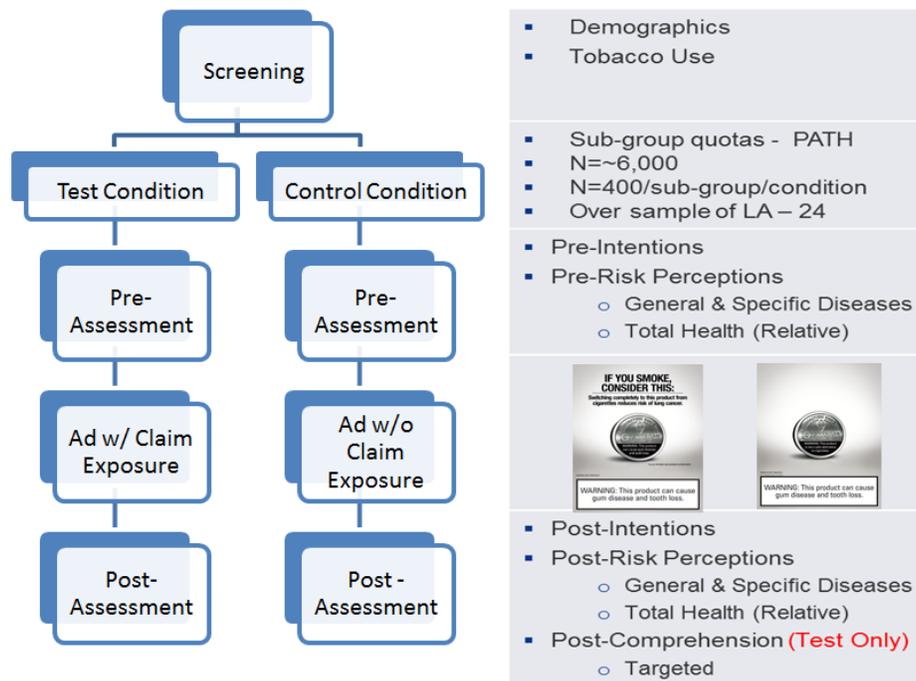
- We chose to begin our claim language with a headline: **“IF YOU SMOKE, CONSIDER THIS.”** We constructed the headline to attract the attention and interest of adult smokers not planning to quit, not nonusers. Research (Belch & Belch, 1993; Hafer & White, 1989) has shown the headline is generally what people first look at in a print ad followed by the illustration.
- We chose to keep the modified risk claim simple by focusing on a single disease – lung cancer. It is a risk reduction claim, relative to continued smoking. It neither states nor implies that the product presents no risk of lung cancer whatsoever.
- We limited by its terms to a single use behavior – that is, switching completely from smoking to this product.

We tested the claims among adult users and nonusers of tobacco products (former and never users) to assess comprehension of the proposed claim and to provide insights into its impact on risk perceptions (absolute and relative) (Figure 14) in the Claim Comprehension and Intentions (CCI) Study (MRTPA, CCI Study Report, Appendix 7.3.2-1).

Based on our study, we demonstrate that:

- The proposed claim language is clear, relevant, believable, and easily understandable; and
- Adult users and nonusers understand the proposed advertising and labeling and are not misled to believe Copenhagen[®] Snuff is without risk.

Figure 14: Basic Outline of the Consumer Comprehension and Intentions (CCI) Study



The CCI Study was a quasi-experimental, repeated measures design, involving 5,871 adult (legal age to use tobacco products [LA] and older) users and nonusers of tobacco products from across the U.S. The study employed multi-modal recruitment methods and included 4,927 main sample participants and 944 over quota participants to increase the base size for LA-24 year olds, a population of interest for FDA.²⁰ We designed this study with adequate sample size to provide 80% statistical power to detect differences in the behavioral intentions of each subgroup between Test (exposure to advertisement with claim) and Control (exposure to advertisement without claim) conditions. To reflect the general population, we matched participants to the U.S. population using major demographic variables (gender, age, race/ethnicity, education, and region) based on quotas from the PATH Study. We assigned participants to one of six subgroups based on their current and prior use of tobacco products.

The subgroups were:

Current Adult Tobacco Users:

- Adult Smokers Planning to Quit (ASPQ)
- Adult Smokers Not Planning to Quit (ASNPQ)
- Adult Dual Users (MST and cigarettes)

²⁰ We chose to oversample this population because FDA in a meeting (Meeting # TC0001446 held on 2/26/2016) on Consumer Perception and Behavior Study Design for MRTPAs had expressed an interest in understanding whether and how modified risk information may affect certain populations such as young adults (age 18-24).

- Adult MST Users

Adult Nonusers:

- Adult Former Users
- Adult Never Users

The pooled LA-24-year-old participants from the main sample and oversample were assigned to either user or non-user subgroups.

We randomly assigned each subgroup to one of two advertising conditions:

- Test Condition, including exposure to an advertisement consisting of the proposed claim, an image of a can of Copenhagen[®] Snuff marketed as Copenhagen[®] Snuff Fine Cut and one of the federally mandated warnings, which were rotated within the study; and
- Control Condition, including exposure to an advertisement consisting of only an image of a can of MST marketed as Copenhagen[®] Snuff Fine Cut and one of the federally mandated warnings, which were rotated within the study, but without the proposed claim.

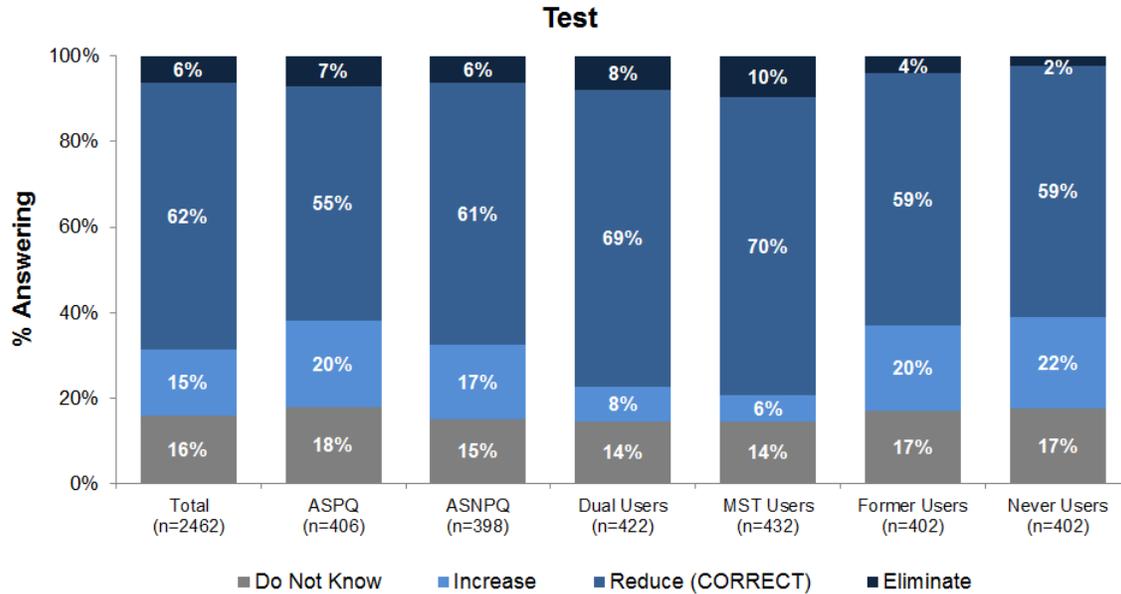
Participants answered questions on risk perceptions before (pre-test) and after (post-test), which helped us understand the influence of participants' incoming beliefs on Test and Control differences and isolate the impact of the proposed claim.

c. Consumers understand the proposed advertising and labeling and are not misled to believe Copenhagen[®] Snuff is without risk.

The CCI Study results demonstrate that study participants understood the modified risk claim in the context of their total health and in relation to other tobacco-related diseases.

Figure 15: Proposed Modified Risk Claim Comprehension

IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer.



Based **only** on the information shown in this ad, smokers who switch completely from cigarettes to Copenhagen® Snuff. Increase the risk of lung cancer, Reduce the risk of lung cancer, Eliminate the risk of lung cancer, Do not know

Source: MRTPA, CCI Study Report, Table 6 (Appendix 7.3.2-1)

Overall, as shown in Figure 15, a clear majority of participants in the Test Condition understood the modified risk claim by selecting the correct response, i.e., “Reduces the risk of lung cancer.” The percentage of participants who responded correctly varied among the user subgroups, ranging from 55% (ASPQ) to 70% (MST Users). A substantial proportion of Dual Users (69%), an audience that may be more likely to quit smoking and exclusively use Copenhagen® Snuff, selected the correct response. The majority of Low Health Literacy²¹ (60%) and Normal Health Literacy (61%) participants identified the correct answer, providing further evidence regarding comprehension of the claim.

The vast majority of study participants (90-98%) who viewed the modified risk claim did not perceive Copenhagen® Snuff as eliminating the risk of lung cancer. To the contrary, only 6% of the total participants who viewed the claim indicated that Copenhagen® Snuff eliminated lung cancer risk. Among current tobacco user subgroups, this perception ranged from 6% (ASN PQ) to 10% (MST users). Tobacco non-user subgroups were less likely to hold this perception, with only 4% of former users and 2% of never users perceiving that Copenhagen® Snuff eliminated lung cancer risk. In a recent study involving modified risk

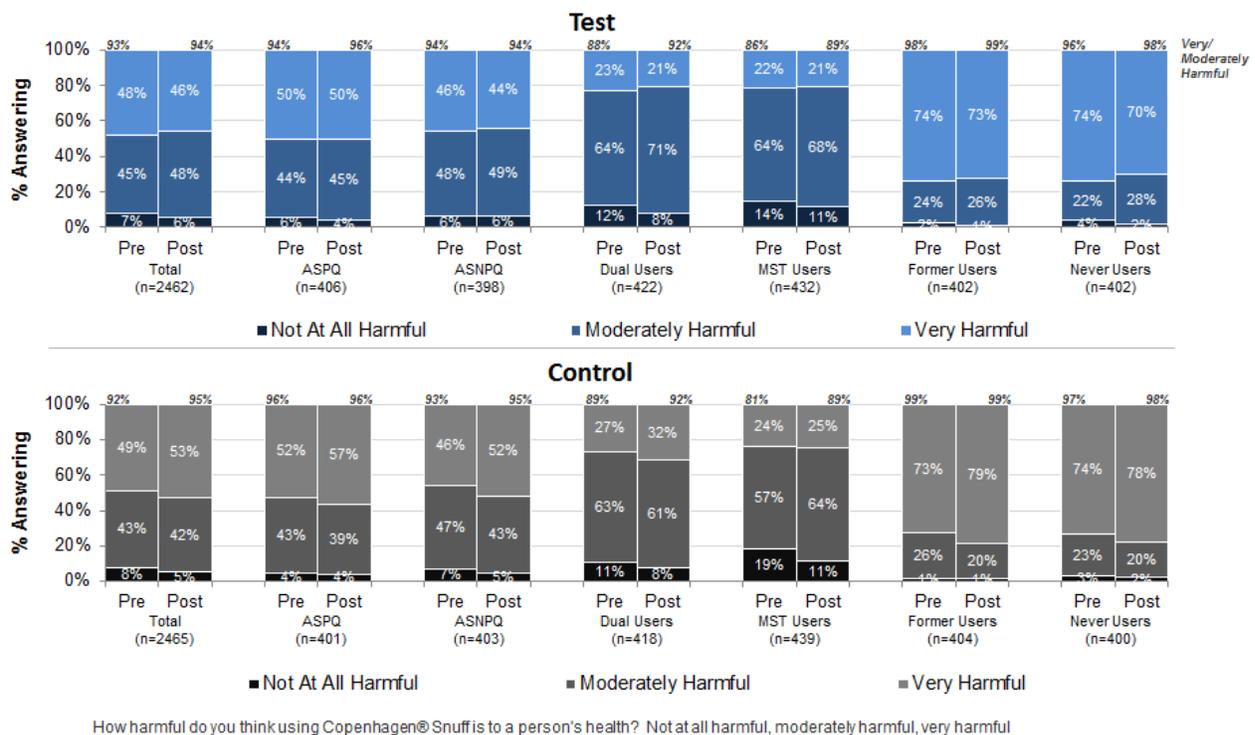
²¹ In the CCI study, participants were asked a single-item health literacy screening question: “How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?” (Single Item Literacy Screener [SILS]; (Morris, MacLean, Chew, & Littenberg, 2006) designed to identify individuals with lower than normal health literacy).

statements associated with a commercial ST product, Fix et al., (2017) reported similar observations; a proportion of the respondents (specific data not reported by the authors) selected “no risk” after viewing the claim.

To further investigate the impact of the claim, we first assessed if the claim led study participants to believe that Copenhagen® Snuff is without harm. Second, we determined whether respondents generalized the reduced risk message to other diseases, beyond lung cancer, by evaluating decreases in risk perceptions of general and specific diseases.

Based on responses to the general harm question, “how harmful do you think using Copenhagen® Snuff is to a person’s health,” we conclude that the modified risk claim did not mislead study participants about the health risks of Copenhagen® Snuff. A vast majority (89%-99%) of participants associated some level of harm (“moderately harmful” or “very harmful”) with using Copenhagen® Snuff after exposure to the proposed modified risk claim. Furthermore, viewing the proposed claim did not increase the perception that Copenhagen® Snuff is “Not at all harmful” in any subgroup (Figure 16). This provides evidence that the claim did not lead people to believe Copenhagen® Snuff presents no harm.

Figure 16: General Harm Associated with Copenhagen® Snuff Pre-Post for Test and Control



Source: MRTPA, CCI Study Report, Table 64 (Appendix 7.3.2-1)
 ASPQ = Adult Smokers Planning to Quit; ASN PQ = Adult Smokers Not Planning to Quit; MST = Moist Smokeless Tobacco

One quarter to one third of adult smokers (~24-32%) did not believe (“strongly disagree” or “disagree”) the proposed claim. See MRTPA, CCI Study Report, Appendix 7.3.2-1, Table 3. These results suggest that pre-existing beliefs about the relative harm of ST products influenced participant responses following exposure to the proposed claim.

We also conclude that the claim did not mislead participants into generalizing the reduced risk message to other diseases beyond lung cancer. We assessed likelihood of six health outcomes (negatively impacts health, mouth cancer, lung cancer, heart disease/heart attack, nicotine addiction and discolored teeth or decay) both in the Test (viewing the advertisement with claim) and Control (without claim) conditions. Overall, there were minimal differences between pre- and post-test responses. If anything, the responses were slightly higher after viewing the proposed claim.

d. The proposed modified risk claim did not alter risk perceptions.

i. Perceived Absolute Risk of Copenhagen[®] Snuff

The CCI Study corroborates previous reports that a large majority of ATCs perceive ST products, including Copenhagen[®] Snuff, as harmful (Figure 16). A vast majority of ATCs (~90%), in both the control and the test conditions prior to viewing the proposed claim, perceived Copenhagen[®] Snuff as moderately or very harmful. Single exposure to the proposed claim did not alter that perception.

Nonusers (Former Users, Never Users and LA-24) overwhelmingly perceived Copenhagen[®] Snuff as very harmful, before and after viewing the proposed claim. A vast majority of MST users (Dual Users and MST Users) perceived Copenhagen[®] Snuff as either moderately harmful or very harmful, but were less inclined than other groups to describe Copenhagen[®] Snuff as very harmful. These ratings did not change after viewing the proposed claim.

Viewing the proposed claim did not increase the proportion of any subgroup that perceived Copenhagen[®] Snuff as “Not at all harmful.” To the contrary, exposure to the proposed claim reduced that proportion in each and every subgroup.

The proposed claim did not alter the risk perception of Copenhagen[®] Snuff for lung cancer. Although the scientific evidence supports the proposed claim, some tobacco users in the study demonstrated a misperception about lung cancer risk. A sizeable proportion of tobacco users (49% ASPQ, 38% ASNPQ, 28% Dual Users, 25% MST Users, 34% LA-24 Users) continued to believe that Copenhagen[®] Snuff was highly likely to cause lung cancer ($\geq 70\%$ “likelihood of lung cancer occurring”) even after viewing the proposed claim (See Section 6.2 of the MRTPA).

ii. Perceived Risk of Copenhagen[®] Snuff Relative to Cigarettes and Other ST Products

In general, across all subgroups, single exposure to the proposed claim did not alter relative risk perceptions. All subgroups, on average, ranked cigarette smoking as only slightly more risky than Copenhagen[®] Snuff. Between 43% and 64% of subgroup participants assigned the same risk to using Copenhagen[®] Snuff as to smoking cigarettes.

Participants rated the perceived risk of lung cancer from use of Copenhagen[®] Snuff as slightly lower than smoking cigarettes, on average. For pre- and post-exposure risk perceptions of cigarette smoking and Copenhagen[®] Snuff, see MRTPA, Appendix 7.3.2-1; Table 56 and 57)

Participants rated the perceived risk of general and specific health outcomes from using Copenhagen[®] Snuff as similar to that of using cigarettes on three of the six items – specifically “Negatively Impacts Health,” “Nicotine Addiction,” and “Discolored Teeth or Decay.” Additionally, participants generally perceived higher risk for mouth cancer with Copenhagen[®] Snuff than smoking, while they perceived risk for lung cancer as only slightly lower than smoking.

Relative to ST use, most CCI Study participants perceived Copenhagen[®] Snuff to be equally risky as other snuff/dip/ST products and did not change their perceptions after exposure to the proposed claim. Nonusers of tobacco (former and never user subgroups) consistently perceived higher risks for each tobacco use behavior than tobacco product user subgroups, both before and after exposure to the claim. Similarly, both tobacco users and nonusers accurately rated the risks of using Copenhagen[®] Snuff to be higher than using nicotine replacement therapies (NRTs), quitting all tobacco use, or never using tobacco products.

These results demonstrate that the proposed claim does not mislead ATCs about the relative risk of Copenhagen[®] Snuff as compared to cigarettes or other ST products.

e. Conclusions – Effect of Marketing on Consumer Understanding and Perceptions

Based on the results of our CCI Study regarding comprehension of the proposed modified risk claim and its impact on risk perceptions, we conclude:

- Adult tobacco users and nonusers (including LA-24 year olds) understand and do not misinterpret the advertising and labeling with the proposed claim.
- Adult tobacco users and nonusers continue to believe that Copenhagen[®] Snuff use poses risk to health after viewing advertising and labeling with the proposed claim and accurately perceived using NRTs, quitting tobacco use, or never using tobacco products as much lower risk options.
- The single exposure to our proposed claim had no effect on perceptions of the health risk of Copenhagen[®] Snuff as compared to cigarettes. Risk perceptions proved consistent with literature findings in failing to differentiate the substantial difference in risk between Copenhagen[®] Snuff and cigarettes.
- The non-MST user subgroups (adult smokers, nonusers and former tobacco users) generally have higher perceived levels of risk than current MST users.

We observe that a single exposure to accurate information, in the form of our proposed claim, did not correct the existing misperceptions regarding Copenhagen[®] Snuff, notwithstanding the fact that participants understood the proposed claim and were not misled by it. These results are unsurprising. Prior published studies (Table 1) have demonstrated that

adult smokers and other adult tobacco users have preexisting and deeply rooted misperceptions about the health risks of ST relative to cigarettes. As suggested in other research, repeated exposures would likely be needed for the information to permanently alter beliefs, intentions, and to have any sustained influence on tobacco use behaviors (Borland et al., 2012).

We propose a postmarket surveillance program that will include both passive and active surveillance activities, to continue to monitor the impact of the proposed modified risk claim on the risk perceptions of users and nonusers of tobacco products.

IV. **POTENTIAL IMPACT TO THE POPULATION AS A WHOLE**

a. Effect on Tobacco Use Behavior among Current Users

Based on our assessment of the likelihood of use of Copenhagen[®] Snuff among various subgroups of current tobacco users after viewing the proposed modified risk claim, we demonstrate that:

- there is some increase in likelihood of use of Copenhagen[®] Snuff, although modest, with greatest use potential among the adult male smoker subgroup;
- while not statistically significant, there is a modest increase in switching behavioral intentions in Adult Smokers Not Planning to Quit;
- while not statistically significant, there is a modest increase in the likelihood of Copenhagen[®] Snuff use in conjunction with other products; and
- there is no statistically significant increase or decrease in the likelihood that users who may have otherwise quit using tobacco products will instead use Copenhagen[®] Snuff.

Also, based on a randomized controlled clinical study and review of the published literature on ST products, we demonstrate that the abuse potential of Copenhagen[®] Snuff is lower than cigarettes and greater or similar to NRT products, specifically nicotine polacrilex gum (NRT gum).

i. We observe a small increase in likelihood of using Copenhagen[®] Snuff among current adult smokers not planning to quit.

The CCI Study (MRTPA, CCI Study Report, Appendix 7.3.2-1) assessed possible changes in tobacco product behavioral intentions (intent to use, try or switch) as a result of viewing the proposed claim. Based on the results of the study, we observe a small increase in likelihood of using Copenhagen[®] Snuff among current adult smokers not planning to quit after exposure to the proposed claim, and adult male smokers expressed greater interest in using the product with the claim. Overall, we believe that a large percentage of current users are unlikely to switch immediately to Copenhagen[®] Snuff. Over time, that percentage may increase, which we would detect through postmarket surveillance.

In the CCI Study, after adjusting for covariates, we observed no statistically significant differences ($p > 0.05$) between the Test and Control conditions in intentions to *try* or *switch* from cigarettes to Copenhagen® Snuff for any tobacco product user subgroup (Table 2). The lack of interest in potential trial and use in adult smokers planning to quit is a favorable outcome suggesting that the proposed claim is not likely to intercept quitting.

Consistent with their stated reluctance to *try* Copenhagen® Snuff, most groups also indicated no change in intention to *use* Copenhagen® Snuff after viewing the advertisement. After adjusting for covariates, we observed a statistically significant difference in intention to use between the Test and Control conditions among adult smokers not planning to quit (ASN PQ) subgroup. Specifically, ASN PQ in the Test condition, after exposure to the proposed claim, reported a modestly higher intention to use than ASN PQ in the Control condition. The effect size for this difference was small (adjusted sample mean [M] = 2.39 vs. adjusted M = 2.26; eta-squared [η^2] = 0.00). We attach little relevance to the finding given the inconsistency with their intention to try Copenhagen® Snuff and small effect size.

Table 2: Composite Scores (unadjusted means) of Responses Related to Copenhagen® Snuff Trial, Use or Switching among Current Tobacco Users

Group	Condition	Intention ¹					
		Intent to Try		Intent to Use		Intent to Switch	
		Pre	Post	Pre	Post	Pre	Post
ASPQ ²	Control (n = 401)	2.43	2.30	2.31	2.20	2.19	2.11
	Test (n = 406)	2.40	2.36	2.29	2.25	2.16	2.11
ASN PQ ³	Control (n = 403)	2.54	2.46	2.41	2.31	2.08	2.06
	Test (n = 398)	2.49	2.48	2.32	2.34*	2.02	2.09
MST ⁴ users	Control (n = 341)	4.36	4.35	4.27	4.18	Not asked since already using MST products	
	Test (n = 356)	4.49	4.37	4.22	4.16		
Dual Users	Control (n = 337)	4.51	4.38	4.22	4.13	3.33	3.27
	Test (n = 336)	4.59	4.54	4.43	4.32	3.51	3.51

Source: Trial – MRTPA, CCI Study Report, Table 7, 16 (Appendix 7.3.2-1)

¹ Values represent the unadjusted average score of responses to statements or questions related to trial or use of Copenhagen® Snuff before (pre) or after (post) reading an advertisement containing the proposed modified risk claim language (Test) or reading and advertisement without the proposed claim language (Control). Participants assigned their agreement on a scale of 1-6 (6=Strongly Agree, 5=Agree, 4=Somewhat Agree, 3=Somewhat Disagree, 2=Disagree, 1=Strongly Disagree) to the following: Trial - I am open to trying Copenhagen® Snuff in the next 30 days; Based on what you know about Copenhagen® Snuff, how likely or unlikely are you to try Copenhagen® Snuff?; Based on what you know about Copenhagen® Snuff, how likely or unlikely are you to try Copenhagen® Snuff if one of your best friends were to offer Copenhagen® Snuff to you?; Use - I would consider using Copenhagen® Snuff more than once. I expect to use Copenhagen® Snuff. It is likely that I will regularly use Copenhagen® Snuff in the next 6 months. Copenhagen® Snuff will be my regular brand of snuff/dip/smokeless tobacco in the next 30 days. Switch -I plan to gradually switch from regular cigarettes to a Copenhagen® Snuff. I plan on Copenhagen® Snuff as a complete replacement for regular cigarettes. I intend on switching from cigarettes to Copenhagen® Snuff in the next six months.

² ASPQ = Adult Smokers Planning to Quit

³ ASN PQ = Adult Smokers Not Planning to Quit

⁴ MST = Moist Smokeless Tobacco

*Statistically significant greater change (pre – post) in intention in the Test Condition relative to the Control Condition after exposure to the claim. (ANCOVA - After Bonferroni adjustment, *p*-values < 0.008 were considered to be statistically significant.)

We further analyzed responses by reviewing the proportion of current users indicating positive affect to try and positive affect to use Copenhagen[®] Snuff.²² We determined the proportion of respondents likely to try Copenhagen[®] Snuff, based on a composite of respondents who scored above the midpoint of the intention to try scale (> 3.5) and who responded “Yes” to the purchase intent question. We applied the same approach to determine the proportion of respondents likely to use Copenhagen[®] Snuff (i.e., those with an intention to use score above the midpoint of the scale and who responded “Yes” to the purchase intent question). We observed (Table 3) a modest increase (relative increase by ~10%) in the proportion indicating a likelihood of future behavior only in the ASNPQ subgroup for the Test condition for both trial and regular use. Upon further examination in only adult male smokers (the audience most likely to use this product) we observe ~20% relative increase in the behavioral intentions, which served as one of the inputs for our population model. See MRTPA, Appendix 7.4.2-4, Table 1. Additionally, young adults (LA-24 year olds) did not exhibit any increase in likelihood of use or try after exposure to claim under the Test Conditions.

Table 3: Proportion of Current Tobacco Users Indicating Likelihood of Trial or Use

Group	Condition	Likelihood of Behavior (%) ¹			
		Intent to Try		Intent to Use	
		Pre	Post	Pre	Post
ASPQ	Control (n = 401)	19.45	17.21	18.70	17.96
	Test (n = 406)	20.44	20.20	21.18	19.21
ASNPQ	Control (n = 403)	20.35	20.35	21.34	19.85
	Test (n = 398)	19.10	20.35	17.84	19.60
MST users	Control (n = 341)	62.17	63.93	48.87	47.84
	Test (n = 356)	65.17	66.01	52.78	52.78
Dual Users	Control (n = 337)	63.80	62.61	52.15	48.80
	Test (n = 336)	68.45	66.67	55.21	52.37
LA-24 Users	Control (n = 377)	32.10	32.63	29.83	28.88
	Test (n = 377)	37.14	36.34	32.46	32.94

Source: MRTPA, CCI Study Report, Tables 59 & 60 (Appendix 7.3.2-1): Try & Use Copenhagen[®] Snuff.

¹Likelihood of behavior was assessed based on a combination of a positive response to intent to purchase Copenhagen[®] Snuff after reviewing the advertisement along with a composite score of >3.5 for intention to try and use.

²² In simplest terms, “positive affect” is a measure of likelihood of future behavior and refers to a current tobacco user subpopulation that, based on their responses to study questions, appears relatively more likely to try or use Copenhagen[®] Snuff, as compared to other current tobacco users expressing some interest.

Although the single exposure to modified risk messaging in the CCI Study demonstrated only modest effects on participants' intentions to use Copenhagen[®] Snuff, there are many factors that can influence the likelihood of change in behavioral intentions, as presented in the Theory of Planned Behavior (TPB) construct. Over 30 years of research on the TPB, originally described by Ajzen in 1985 (Ajzen, 1985), has shown that there are three primary factors – (attitude toward the behavior, social norm, and perceived behavioral control) – that lead to change in intentions and ultimately behaviors (Godin & Kok, 1996).

Overall, a cigarette smoker will internally process the modified risk message through the cognitive schema developed over his/her lifetime exposure to public health messages regarding ST products and mistrust of industry, all of which will affect a willingness to change attitudes and beliefs enough to manifest into behavioral intentions to use Copenhagen[®] Snuff. Thus, misperceptions may pose a barrier to immediate switching from cigarette smoking to using Copenhagen[®] Snuff. Communicating accurate risk information about Copenhagen[®] Snuff, however, is a necessary first step.

Preexisting and deeply rooted misperceptions about the health risks of ST products relative to cigarettes may mediate the impact of a single exposure to the proposed claim on attitudes toward a perceived health benefit of switching from cigarette smoking to Copenhagen[®] Snuff. Adding further complexity, a cigarette smoker's attitude toward a modified risk message may be influenced by believability of the claim itself due to public opinion about the tobacco industry and decades of public health messaging against tobacco products and ST products in particular (Fix et al., 2017). These findings, that believability influences the impact of a tobacco product risk claim, are consistent with the principles outlined in the TPB.

Taken together, it is not surprising that we did not observe more immediate and extensive changes in behavioral intentions to try or use Copenhagen[®] Snuff, based on a single exposure to the proposed claim. We contend that long-term dedicated efforts that responsibly deliver the proposed modified risk message will be necessary to change tobacco consumers' attitudes, subjective norms, and perceived behavioral controls. Consistent and accurate messaging from all key stakeholders (e.g., tobacco product manufacturers, public health, and regulatory agencies) will be needed to maximize the likelihood of an attitude change toward ST products and, ultimately, complete switching to Copenhagen[®] Snuff.

ii. We found no statistically significant increase or decrease among ATCs with respect to the likelihood of dual use involving Copenhagen[®] Snuff.

Some level of dual use can be expected as ATCs transition from adopting Copenhagen[®] Snuff to switching completely; however, we cannot predict the duration of the transition period for Copenhagen[®] Snuff. The transition from cigarettes to exclusive use of Copenhagen[®] Snuff will likely depend on several factors, both internal (e.g., ATCs overcoming misperceptions about the health risk of Copenhagen[®] Snuff relative to cigarettes) and external (e.g., potential regulatory policies), which can best be assessed through postmarket surveillance.

Our CCI Study indicated no statistically significant differences in intentions to dual use between the Test and Control conditions for any applicable subgroups, after adjusting for

covariates.²³ Of note, the likelihood of dual use among young adults (LA-24 year olds) remained unchanged after exposure to the proposed claim, the proportion with “positive affect” or likelihood of future behavior remained the same 27.58% before and after viewing the proposed claim. Both adult smokers planning to quit and not planning to quit subgroups exhibited a lower likelihood of dual use.

iii. There is low likelihood that ATCs who adopt Copenhagen[®] Snuff will switch to or switch back to other tobacco products that present higher levels of individual health risk.

In a premarket setting, it is difficult to ascertain whether or to what extent users who adopt Copenhagen[®] Snuff once marketed with the proposed claim would switch to cigarettes or another higher risk tobacco product. Direct evidence of this theoretical switching to other tobacco products that present higher levels of individual health risk will not be available until FDA authorizes Copenhagen[®] Snuff to be marketed with the proposed claim.

In general, tobacco users (except for adult male smokers) in our CCI Study expressed little interest in adopting Copenhagen[®] Snuff, even after viewing the proposed claim. To the extent tobacco users do not adopt Copenhagen[®] Snuff, the question of switching back to cigarettes is irrelevant.

Currently available evidence from the literature is inadequate to infer either the presence or absence of a causal relationship between ST use and subsequent smoking. We do not anticipate that adult smokers who adopt Copenhagen[®] Snuff when marketed with the proposed claim would switch back to exclusive cigarette smoking, particularly as they internalize accurate beliefs about the risk differential between Copenhagen[®] Snuff and cigarettes. If anything, it is reasonable to surmise that the proposed claim will discourage users of Copenhagen[®] Snuff from switching or reverting back to cigarettes. We will monitor such behaviors during postmarket surveillance.

iv. We observed no statistically significant increase or decrease in the likelihood that users who may have otherwise quit using tobacco products will instead use Copenhagen[®] Snuff.

Current scientific evidence does not lead us to conclude that marketing Copenhagen[®] Snuff with the proposed claim would hinder a smoker’s attempt to quit smoking. Our CCI Study demonstrates that the proposed claim does not substantially change a consumer’s intentions to quit all tobacco. While we noted a statistically significant difference ($t = -2.66$, $p = 0.008$) between the Test and Control conditions for intentions to quit smoking in the ASPQ group based on a simple t-test, the magnitude of this difference was small. Notably, the direction of the change is also important when assessing these results. The test condition showed an *increase* in intention to quit smoking pre-test to post-test ($M = 0.04$), and the control condition showed a greater increase in intention to quit smoking ($M = 0.09$). The small

²³ This was only asked of current cigarette smokers, regardless of current MST use. Also, they were asked specifically about intention to dual use cigarettes and Copenhagen[®] Snuff.

differences may be attributed to variability between the groups. Using a more robust logistic regression model incorporating key behavioral factors (i.e., product use behavior), these differences were no longer statistically significant. We observed no statistically significant differences between the test and control conditions among current MST users (either exclusive or dual users). Overall, these results indicated little reason to expect adverse impacts on smoking cessation trends, but we will monitor for such impacts under real-world conditions through our proposed postmarket surveillance program.

v. Actual use behavior for Copenhagen[®] Snuff is well established, stable, and not likely to change.

Copenhagen[®] Snuff has been on the market for many decades and the actual use behavior is stable and well established (MRTPA, Section 3.2). Overall, Copenhagen[®] Snuff consumers use about half a can per day with use occasions of about six to nine times per day, each portion size being about 2-2.5 grams kept in the mouth for about 30-40 minutes. We do not anticipate changes in this topography of use in response to the proposed modified risk claim. Even if there was going to be a change in topography of use, it would be difficult to assess potential effects on real-world topography of use in a premarket setting, therefore we will monitor any potential impacts during postmarket surveillance.

We do present multiple lines of supporting evidence for MST consumers (including exclusive and dual users) and current Copenhagen[®] Snuff consumers, demonstrating our ability to assess actual use behavior for a range of relevant use behaviors upon authorization of the proposed claim under real-world settings.

We present an overview of the behavioral measures that were obtained from a variety of studies, including NSDUH and PATH study data, in [Table 4](#). While these studies differed in several respects (e.g., definitions of MST, sampling methods, study populations, mode of survey administration, definitions of measures, and wording of questions), collectively and complemented by published literature, they provide a comprehensive view of conditions for use and actual use behavior.

Table 4: Conditions for Use and Actual Use Behavioral Measures by Study

Measure	Population Assessment of Tobacco and Health (PATH, 2013-2014)	National Survey on Drug Use and Health (NSDUH, 2014)	ALCS Tracking Study (2015-2017)	ALCS Consumer Behavior Study (2013)	ALCS Clinical Study (2017)
<i>Section 3.2.1: The Conditions for Using the Tobacco Product</i>					
Length of time a dip is kept in mouth				✓	✓ ¹
<i>Section 3.2.2: How Adult Consumers Actually Use the Product</i>					
Number of days using MST (in past 30)	✓	✓	✓	✓	
Portion size					✓ ¹

Measure	Population Assessment of Tobacco and Health (PATH, 2013-2014)	National Survey on Drug Use and Health (NSDUH, 2014)	ALCS Tracking Study (2015-2017)	ALCS Consumer Behavior Study (2013)	ALCS Clinical Study (2017)
Number of daps or use occasions per day	✓			✓	✓ ¹
Number of cans of MST used per day			✓		
Section 3.2.3: Concurrent Use of Multiple Products Containing Nicotine or Tobacco					
Dual use ² of MST and cigarettes	✓	✓	✓		
Number of days smoking in past 30 days (among dual)	✓	✓	✓	✓	
Cigarettes smoked per day (among dual)	✓	✓	✓	✓	

¹ Measure was limited to four-hour *ad libitum* period.

² Dual use is defined as reported past 30-day use of MST and past 30-day use of cigarettes. While a sizeable proportion of MST users consume other tobacco products, we focus our discussion on dual use of MST with cigarettes because this is the largest proportion among dual users.

Limitations of the data sources include recall bias and generalizability. While we recognize these limitations, we draw on these diverse studies with complementing features to provide a more comprehensive view of MST use and to infer actual use behavior of Copenhagen[®] Snuff with the claim.

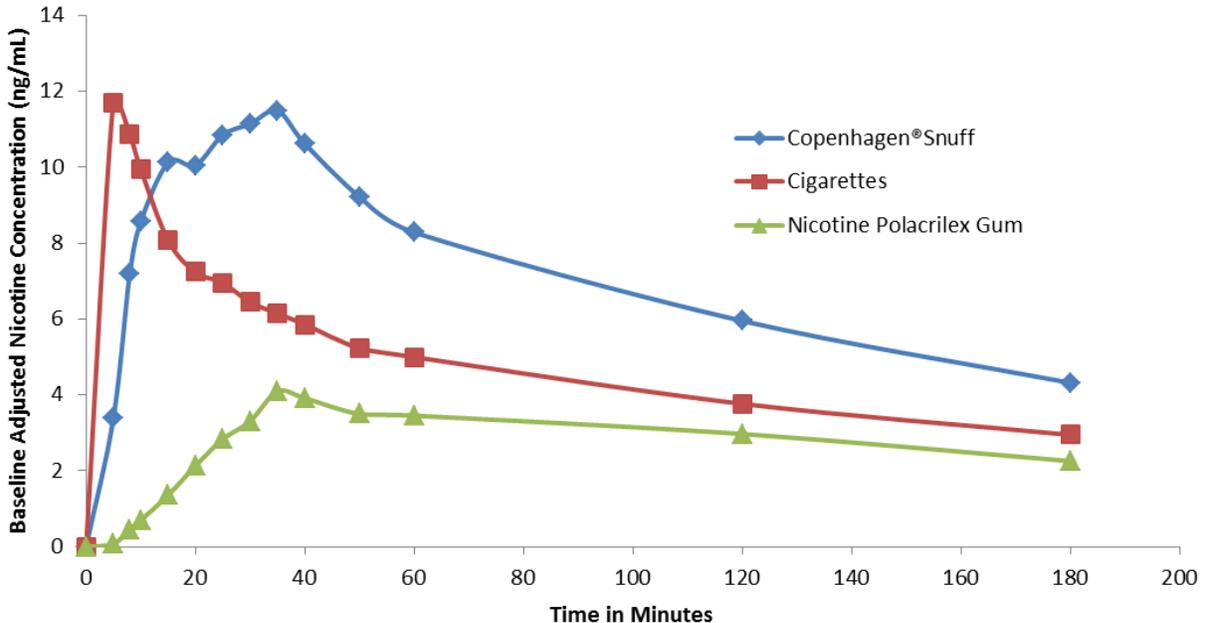
vi. Copenhagen[®] Snuff exhibits greater than, or similar, abuse potential to NRT gum, but lower abuse potential than cigarettes.

We investigated the abuse liability of Copenhagen[®] Snuff through review of published literature and clinical research. We conducted a randomized, controlled, three-way, crossover clinical study characterizing nicotine pharmacokinetics, [Figure 17](#), and subjective effects for Copenhagen[®] Snuff (manufactured as the grandfathered product), own brand cigarettes and NRT gum (MRTPA, Pharmacokinetic Study with Subjective Effects Report, Appendix 7.3.1). Based on the pharmacokinetic profile of Copenhagen[®] Snuff and subjective effects measured in our study, we conclude that the abuse potential of Copenhagen[®] Snuff is greater than, or similar to that of NRT products, but less than that of cigarette smoking.

FDA-commissioned recommendations published by the former Institute of Medicine (now National Academy of Medicine) provide context for interpreting this finding. According to the Institute of Medicine Committee on Scientific Standards for Studies on Modified Risk Tobacco Products, “[t]he MRTP should be somewhat more reinforcing than nicotine

replacement therapies but perhaps less reinforcing than conventional cigarettes.”²⁴
Copenhagen[®] Snuff satisfies this criterion, because our data indicate that it is at least as reinforcing as NRT gum but less reinforcing than cigarettes.

Figure 17: Nicotine Pharmacokinetic Profile for Copenhagen[®] Snuff Relative to Own Brand Cigarettes and NRT Gum



Source: MRTPA, Pharmacokinetic Study with Subjective Effects, Table 9 (Appendix 7.3.1).

vii. Conclusions – Effect on Tobacco Use Behavior among Current Users

Overall, we expect a minimal change in tobacco product use behaviors among current users, based on the CCI Study results. We anticipate that the emphasis on “complete switching” and prolonged exposure to marketing information containing the modified risk claim will, over time, contribute to adult cigarette smokers internalizing the accurate modified risk claim and adjusting their prior beliefs, and encourage them to switch to Copenhagen[®] Snuff instead of cigarettes.

Consistent with Institute of Medicine recommendations, the abuse potential of Copenhagen[®] Snuff is greater than, or similar to, that of NRT products and lower than cigarettes..

Our postmarket surveillance will monitor for actual impacts on tobacco use behavior among current users under real-world conditions.

²⁴ Institute of Medicine (2012). Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, DC: The National Academies Press.

b. Effect on Tobacco Use Behavior among Nonusers

Our MRTPA demonstrates that market authorization of the proposed claim should result in minimal change in likelihood of use of Copenhagen[®] Snuff among nonusers based on our results from the CCI Study, our analysis of national survey data related to ST initiation and use among youth, and our review of published scientific literature.

We designed the proposed claim with emphasis on “IF YOU SMOKE, CONSIDER THIS” to draw the attention of adult smokers – not nonusers.

Our advertising is intended to reach smokers while minimizing its reach to unintended audiences including youth. We minimize the reach of marketing communications to unintended audiences as follows:

- Print advertisements are accompanied by the required rotating warnings.
- We limit print advertising to newspapers, magazines, and other publications that meet the criteria of an “adult publication” under FDA’s definition.²⁵
- We verify the age of consumers *and* have them certify that they are smokers and/or smokeless tobacco users *before* they can receive one-to-one marketing communications like direct mail, access any brand website, or enter a brand marketing event.
- At retail, our trade programs with tobacco retailers have multiple safeguards designed to prevent underage access to tobacco products. These include displaying our products only in a non-self-service location, training store personnel to require age verification before selling tobacco products, and posting signs that prohibit underage sales and encourage adults not to purchase tobacco products for underage use.

It is difficult to predict the impact of our proposed claim on various nonuser groups. We propose a comprehensive postmarket surveillance program to monitor for unanticipated and undesirable use of Copenhagen[®] Snuff in nonusers, particularly youth. The postmarket surveillance program will include both passive and active surveillance activities, a series of postmarket studies and population modeling.

i. We expect no increase or decrease in the likelihood of initiation of Copenhagen[®] Snuff use in adult nonusers (never and former users), LA-24 nonusers and youth.

In the CCI Study, we observed no statistically significant ($p > 0.05$) increase or decrease in the intent to try or use Copenhagen[®] Snuff among adult nonusers, particularly young adults (LA-24 year olds), in response to the proposed modified risk claim. In addition to measuring intention to try and use, we also analyzed the likelihood to try and use by combining positive behavioral intentions (composite score >3.5) with intention to purchase. Before exposure to the proposed claim, nonusers in both the test and control conditions expressed very low

²⁵ 21 CFR §1140.32(a)(2).

intention to try or use Copenhagen[®] Snuff. After exposure to the proposed claim, nonusers remained disinterested, as measured by unchanged intentions to try or use Copenhagen[®] Snuff (Table 5). Less than 3% of participants in any non-user study group indicated a likelihood to try Copenhagen[®] Snuff (Table 6). We observed no significant ($p > 0.05$) changes in likelihood of initiation among LA-24 nonusers.

Overall, there is no reason to expect an increase in initiation of Copenhagen[®] Snuff when marketed with the proposed modified risk claim, based on the lack of interest in Copenhagen[®] Snuff by the population of nonusers (adults and young adults LA-24) after exposure to that claim. We do not anticipate youth initiation rates for Copenhagen[®] Snuff to exceed rates currently observed for the ST category. Data for smokeless tobacco use and risk perceptions among youth provide additional insights supporting this conclusion.

Table 5: Average Composite Scores for Intention to Try and Use Copenhagen[®] Snuff among Adult Nonusers

Group	Condition	Intent to Try ¹		Intent to Use ²	
		Pre	Post	Pre	Post
Never Users	Control (n = 400)	1.4	1.3	1.3	1.3
	Test (n = 402)	1.3	1.2	1.3	1.2
Former Users	Control (n = 404)	1.3	1.3	1.3	1.2
	Test (n = 402)	1.4	1.3	1.3	1.3
Nonusers LA-24	Control (n = 403)	1.4	1.4	1.3	1.3
	Test (n = 401)	1.5	1.4	1.4	1.4

Source: MRTPA, CCI Study Report, Appendix 7.3.2-1; Table 7 (Intention to Try Copenhagen[®] Snuff); Table 16 (Intention to Use Copenhagen[®] Snuff).

¹ Intention to try was a composite measure of mean ratings from three items (I am open to trying Copenhagen[®] Snuff in the next 30 days; 2) Based on what you know about Copenhagen[®] Snuff, how likely or unlikely are you...? a) To try Copenhagen[®] Snuff b) To try Copenhagen[®] Snuff if one of your best friends were to offer Copenhagen[®] Snuff to you), each asked before and after viewing the advertisement for Copenhagen[®] Snuff. The first item was measured on a six-point scale, ranging from Strongly Disagree to Strongly Agree. The other two items were also measured on a six-point scale, ranging from Definitely Not to Definitely.

² Intention to use was a composite measure of mean ratings from four items; 1) I would consider using Copenhagen[®] Snuff more than once. 2) I expect to use Copenhagen[®] Snuff. 3) It is likely that I will regularly use Copenhagen[®] Snuff in the next six months. 4) Copenhagen[®] Snuff will be my regular brand of snuff/dip/smokeless tobacco in the next 30 days. Each item was measured on a six-point scale, ranging from Strongly Disagree to Agree.

Table 6: Proportion of Adult Nonusers Indicating Likelihood of Trial or Use

Group	Condition	Likelihood to Try ¹		Likelihood to Use ¹	
		Pre	Post	Pre	Post
Never Users	Control (n = 400)	2.25%	2.00%	2.25%	2.00%
	Test (n = 402)	2.49%	1.74%	2.49%	1.74%
Former Users	Control (n = 404)	1.73%	1.73%	1.98%	1.73%
	Test (n = 402)	2.99%	2.49%	2.49%	2.74%
Nonusers LA-24	Control (n = 403)	2.48%	1.74%	2.73%	1.74%
	Test (n = 401)	1.75%	2.24%	2.74%	2.00%

¹Positive affect or likelihood of future behavior was assessed based on a combination of a positive response to intent to purchase Copenhagen[®] Snuff after reviewing the advertisement along with a composite score of > 3.5 for intention to try and use. MRTPA, CCI Study Report, Appendix 7.3.2-1, Table 59 Positive Affect: Try Copenhagen[®] Snuff; MRTPA, CCI Study Report, Appendix 7.3.2-1, Table 60 Positive Affect: Use Copenhagen[®] Snuff

Over the past decade, the overall prevalence of ST use in youth, young adults, and older consumers has been low in the U.S. (Figure 18). Specifically, the overall prevalence of ST use in 12-17 year olds and 18-25 year olds is trending downward. A comprehensive review of the literature indicates a much lower prevalence of ST use among youth and young adults compared to smoking.

According to data collected as part of the Monitoring the Future (MTF) study (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016), a long-term study of American adolescents, college students, and adult high school graduates through age of 55 years, the use of ST has been decreasing gradually, and 30-day prevalence is now approximately half the peak levels reached in the mid-1990s. Daily usage rates in 2015 were 0.8%, 1.6%, and 2.9% for Grades 8, 10, and 12, respectively (Johnston et al., 2016). Minor reductions in past-month ST use were also reported in results from the Youth Risk Behavior Survey, a biannual, in-school survey conducted by the Centers for Disease Control and Prevention (www.cdc.gov/healthyyouth/data/yrbs/index.htm). According to the Youth Risk Behavior Survey, past-month use of ST declined slightly from 11.4% in 1995 to 8.8% in 2013 (Kann et al., 2014).

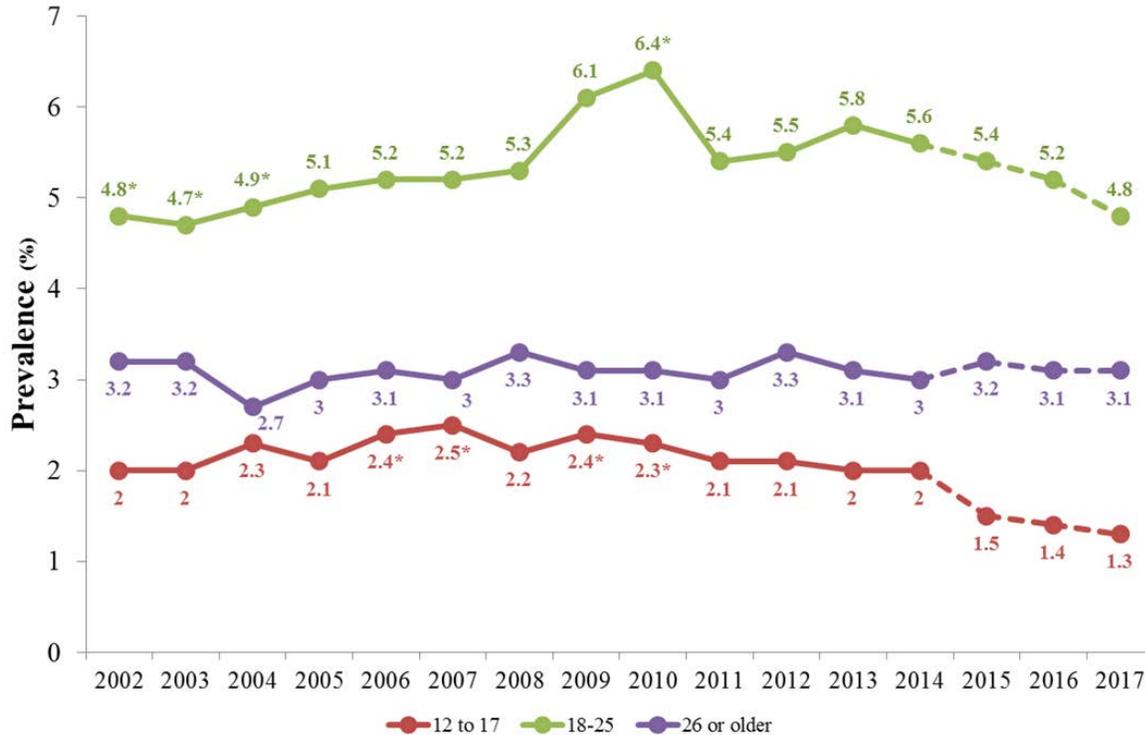
Persoskie et al. (2017) used data from Wave 1 (2013 to 2014) of PATH, a large, national study, to present information on prevalence of adolescent ST use. The responses from youth (age: 12 to 17 years) indicated that 1.6% had used ST within the past 30 days, and an additional 3.2% had used ST outside of the last 30 days.

Smaller regional surveys of tobacco use in adolescents and young adults have conflicting information on the trend of ST use. For example, a study of New York City high school students (Elfassy, Yi, & Kansagra, 2015) reported increased ST use (defined as using at least once in the past 30 days) between 2001 and 2013 overall (1.1% to 4.4%, $p < 0.001$), among

both nonsmokers of cigarettes (0.2% to 1.9%, $p < 0.001$) and among cigarette smokers (4.2% to 21.2%, $p < 0.001$). Over the same time period, prevalence of cigarette smoking declined from 17.6% to 8.2%.

Figure 18: Past Month Smokeless Tobacco Use Among People Aged 12 Years or Older, by Age Group: Percentages, 2002-2017

Sources: 2002-2014: Adapted from Behavioral Health Trends in the United States: Results from the 2014 National



Survey on Drug Use and Health (2015); Figure 23, page 18. 2015-2016: Center for Behavioral Health Statistics and Quality (2017). National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD; Table 2.29. B 2017: Center for Behavioral Health Statistics and Quality (2018). National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD; Table 2.29. B

Notes: 2015-17 and prior years data are not comparable due to the inclusion of snus in the definition of ST. Before 2015, smokeless tobacco included chewing tobacco or snuff/dip. In 2015, 2016, and 2017, smokeless tobacco includes snuff, dip, chewing tobacco and snus.

*Denotes a statistically significant difference between this estimate and the 2014 estimate at the .05 level. Significance is indicated only for years 2002 to 2014.

Also over the past decade, an increasing proportion of youth perceive ST products as less hazardous than cigarettes. Data from the MTF study reveal that, in 2002, 46.9% of 10th graders perceived “great risk” in using ST regularly versus 64.3% who perceived “great risk” for smoking one or more packs of cigarettes – a 17.4 percentage point difference. By 2017, this difference had widened to 29.1 percentage points, with 40.7% and 69.8% of 10th graders, respectively, reporting “great risk” in using ST versus smoking cigarettes. Despite these

differences, data from the MTF study indicate that prevalence of past 30-day ST use among 8th, 10th, and 12th graders combined remained generally stable and even indicate a directional decline from 5.2% in 2002 to 3.5% in 2017 (Miech et al., 2017).

Taken together, these data show that the prevalence of ST use remained low over the past decade among youth, notwithstanding increasing recognition by youth that ST use is less hazardous than cigarette smoking. While coincident time trends must be interpreted with caution, these patterns certainly do not suggest that providing accurate relative risk information is likely to increase youth use of ST products like Copenhagen[®] Snuff beyond current rates. If anything, these patterns suggest that the proposed modified risk claim is unlikely to substantially influence ST product use among youth.

A variety of factors influence youth ST product trial and use. Among children and adolescents, familial use of ST products is strongly related to trial and initiation, while in young adults, peer use has a greater influence. Trial and regular ST product use are also related to accessibility and other risky or thrill-seeking behaviors.

Given the role of the factors influencing trial and use of ST products, marketing Copenhagen[®] Snuff with the proposed claim is unlikely to impact initiation in youth and young adults beyond currently-observed rates for the ST product category.

In summary, results from our CCI Study among nonusers and observations from national surveys among youth do not lead us to conclude that marketing Copenhagen[®] Snuff with the proposed claim will increase initiation among non-user groups. We plan to monitor for such effects in our postmarket surveillance program.

ii. We expect no increase or decrease in the likelihood that nonusers who may adopt Copenhagen[®] Snuff will switch to other tobacco products that present higher levels of individual health risks (i.e., cigarettes).

In a premarket setting, it is difficult to ascertain whether or to what extent nonusers who may adopt Copenhagen[®] Snuff, if marketed with the proposed claim, would subsequently switch to cigarettes or another higher risk tobacco product. Direct evidence of this theoretical behavior will not be available until Copenhagen[®] Snuff is marketed with the proposed claim, following FDA authorization. We will monitor this behavior (sometimes referred to as the *gateway effect*) during postmarket surveillance.

Nonusers in our CCI Study expressed no interest in adopting Copenhagen[®] Snuff, even after reviewing the modified risk claim. This suggests that the likelihood of nonusers initiating smokeless use, then switching to cigarettes is an irrelevant consideration.

The existing literature on the potential of ST as a “gateway” to cigarette smoking is conflicting. While there are strong associations between risky behaviors, debate continues as to whether less risky behaviors present a causal mechanism that acts as a “gateway” to more risky behaviors. Published literature does not suggest an increase in the likelihood that nonusers (adult and youth) will switch to cigarettes after adopting ST, after adjusting for the factors that typically influence tobacco product use behavior.

The research of Kozlowski, O'Connor and colleagues brings to light the importance of accounting for prior cigarette use when assessing associations.²⁶ Indeed, studies that include assessments of exclusive ever ST users at baseline (i.e., those who report only having ever used ST relative to other tobacco products) allow for stronger inferences about temporality to be drawn with respect to the question of the likelihood of nonusers adopting ST and switching to cigarette smoking.

A recent study by Watkins, Glantz, and Chaffee (2018) provides evidence relative to exclusive ever ST users among youth never-smokers using nationally representative PATH data. According to their findings, ever use of *ST only* at baseline was not predictive of the onset of cigarette smoking at Wave 2 in the adjusted models. In addition, the associations between past 30-day ST use (with or without other non-cigarette use) at Wave 1 and ever and past 30-day cigarette smoking at Wave 2 were also *not* statistically significant. Various baseline risk factors for smoking remained significant in their models, and inclusion of marijuana use in sensitivity analyses reduced the magnitude of associations. These findings suggest no specific relationship linking ST use with smoking onset and are in line with the common liability model (Hicks, Iacono, & McGue, 2012).

Analyzing four waves of the National Longitudinal Study of Adolescent Health, Kaufman and colleagues estimated transition probabilities for cigarette and ST use among a cohort of 7th-12th grades into young adulthood (Kaufman, Land, Parascandola, Augustson, & Backinger, 2015). Among those who reported using *ST only* (past 30-day use, exclusive of cigarette smoking) at a given time point, the estimated probability of transitioning to cigarette smoking over a 1-year period was 4.6%, which was less than the 5.6% probability among those using neither ST nor cigarettes. A similar pattern was observed among white males: The probability of transitioning to cigarette smoking over one year among those who used *ST only* at a given point in time was 6.5%, which was less than 7.8% among those using neither product. Consistent with Watkins et al. (2018), these results show that those reporting *ST only* at a given time point were *not* more likely to report smoking at follow-up compared to users of neither ST nor cigarettes. Results of these studies run counter to gateway concerns.

Recent studies using longitudinal data from the Tobacco Use Supplement of the Current Population Survey (TUS-CPS) provide evidence contrary to the gateway effect. Wang et al. (2016) pooled data from three waves of TUS-CPS. Among adult non-daily smokers at baseline, those who reported current ST use were significantly less likely to transition from non-daily to daily cigarette smoking over 12 months compared to non-current ST users. Chang et al. analyzed ST use and cigarette smoking transitions using the TUS-CPS (2010 to

²⁶ Kozlowski, O'Connor and colleagues also raise the relevance of the sequence of product use, cf., Kandel, (2003). Assessing likelihood of nonusers adopting ST and switching to cigarette smoking, presupposes ST use comes first. Research suggests that this sequence is not the case for many ST ever users. Using the Cancer Control Supplement to the 1987 National Health Interview Survey to analyze tobacco use status and history among males age 23 to 34-years old who had ever used ST, Kozlowski et al. (2003) reported that 77.2% were classifiable as "non-gateway users" since they had only used ST or had smoked cigarettes first. Similar results were reported by O'Connor et al. (2005) and Rodu and Cole (2010) analyzing large national datasets in later years. These observations are consistent with the lower mean age of first use reported for cigarette smoking (18 years of age) compared to ST use (20.4 years of age) (Lipari, Ahrnsbrak, Pemberton, & Porter, 2017). These data suggest that many ST users do not exhibit a product use pattern consistent with gateway.

2011) (Chang, Levy, & Meza, 2017). The proportion of males who switched from ST to cigarettes (1.4%) reported in this study was comparable to the proportion who switched from cigarettes to ST (1.2%), suggesting that transitions between ST use and cigarette smoking may be bi-directional. Additionally, our analysis comparing PATH Waves 1 and 2 found that only 1% of new cigarette smokers at Wave 2, identified as ST users in Wave 1. By contrast, the largest proportion (74%) of new cigarette smokers at Wave 2 self-reported as never tobacco users in Wave 1.

The associations between risky behaviors suggest common risk and protective factors underlie risky behaviors, including tobacco use [cf., Jackson et al. (2012)]. While certain factors particularly apply to ST (e.g., significantly more prevalent among males), many are consistent with those identified in the published literature that pertain to cigarette smoking (cf., Turner et al. (2004)). The shared risk and protective factors for tobacco use and the observation that individuals are prone to engage in multiple risk behaviors suggest a broader integrating framework for understanding tobacco use behavior. One theory, the common liability theory, identifies psychological and heritable factors contributing to risky behavior, substance use disorders, and problem behaviors (Hicks et al., 2012; Holman, Bricker, & Comstock, 2013; Jessor & Turbin, 2014). The common liability theory uses socio-cultural and heritable cues to explain adolescent and young adult initiation into tobacco, alcohol, and other drugs, thereby constructing a general set of risk factors (Hicks et al., 2012). Consistent with this theory, with a few exceptions, the factors associated with ST use tend to not be unique to ST.

A range of factors has been associated with ST use, many common to other risk behaviors. With respect to drawing inferences to the potential effect of marketing Copenhagen[®] Snuff with the proposed modified risk claim, the literature suggests that ST use behavior may be more likely associated with personal, social, and environmental influences than with a specific tobacco product marketed with the proposed modified risk claim.

In summary, although there is an association between ST use and cigarette smoking, research relevant to a gateway effect is mixed and has not established a causal link. We believe that the best way to address this concern is through postmarket surveillance taking into account the many factors (e.g., peer pressure, marketing and advertising, future regulatory policies) that may influence product use behavior in the real world.

iii. There is no evidence that former users of tobacco products will reinitiate use with Copenhagen[®] Snuff.

We present evidence that former tobacco product users are not likely to reinitiate use with Copenhagen[®] Snuff. We observed no significant ($p > 0.05$) increase in intentions to try and use Copenhagen[®] Snuff among former tobacco product users after reviewing the proposed claim in our CCI Study (MRTPA, CCI Study Report, Appendix 7.3.2-1, [Table 6](#)). The published literature on this behavior pattern for ST use in general, is sparse.

iv. Conclusions – Effect on Tobacco Use Behavior Among Nonusers

We conclude the following, based on the results of our CCI study in nonusers of tobacco products (and also nonusers LA-24) and our comprehensive review of the published scientific literature and analyses of national survey data:

- There is low likelihood that former and never users of tobacco products, including young adult (LA-24 year old) nonusers, will adopt Copenhagen[®] Snuff in the presence of advertising and labeling materials with the proposed claim.
- There is low likelihood that marketing Copenhagen[®] Snuff with the proposed claim will increase youth initiation of the product beyond the current rates observed for the ST category or change the factors influencing youth ST use.
- With regard to a gateway effect, we have no evidence that nonusers would adopt Copenhagen[®] Snuff when marketed with the proposed claim and then switch to more harmful tobacco products. Literature reports regarding association between ST use and cigarette smoking are conflicting and do not establish a causal relationship. In youth, there appears to be greater likelihood that cigarette smoking will lead to ST use than that ST use will lead to cigarette smoking.
- Youth already perceive differences in the relative risks of ST and cigarettes. Despite these differences, the prevalence of ST use among youth has remained stable. These patterns suggest that communicating the proposed modified risk claim is unlikely to substantially influence ST use among youth.
- Overall, we anticipate minimal unintended consequences among nonusers from marketing Copenhagen[®] Snuff with the proposed claim. Direct evidence of underage use and nonusers adopting Copenhagen[®] Snuff can only be obtained under real-world conditions during postmarket surveillance.

c. Estimating the Impact on the Population as a Whole

The statute requires applicants to demonstrate that marketing a modified risk product 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.” FD&C Act §911(g)(1)(B). Computational models can assist in predicting the potential impact of changes in tobacco product use behavior on population health.

We developed and validated a dynamic population model (MRTPA, Population Model, Appendix 7.4.1) to estimate the overall impact of market authorization of the proposed modified risk claim on the population as a whole, including users and nonuser of tobacco products.

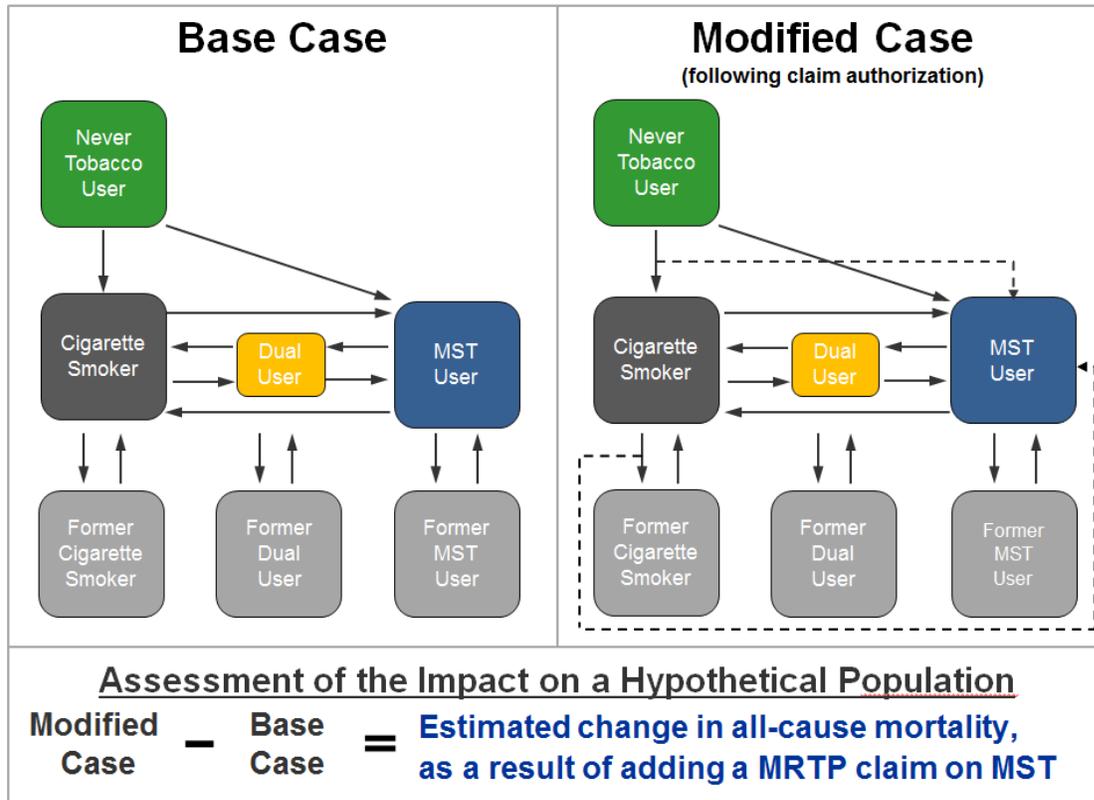
We integrate data from our linked mortality analyses (MRTPA, Linked Mortality Analysis, Appendix 7.4.1) and transition probabilities (derived from the CCI study based on a single exposure to the claim) into our population model to estimate 93,000 premature deaths prevented from market authorization of the proposed modified risk claim.

Predictive computational modeling is a highly technical field with a lexicon derived from mathematics, statistics, epidemiology, and other disciplines. Below, we provide a technical synopsis of our model, focusing on its framework and applications, results, and assumptions and limitations.

i. Framework and Applications of Our Model

Our model estimates the overall impact of market authorization of the proposed modified risk claim on the population as a whole, including users and nonuser of tobacco products. To develop and validate our model, we followed the best practices described by the Modeling Good Research Practices Taskforce, a joint task force developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and the Society for Medical Decision Making (SMDM). The model includes 30 potential transitions and a simplified version is shown in [Figure 19](#). We estimate the benefit based on the difference in mortality between a scenario representing the world as it exists today (Base Case) and a most likely scenario (Modified Case), representing a possible outcome upon FDA authorization of the modified risk claim. We based the estimate on empirical evidence from (1) the Linked Mortality Analysis regarding the risk reduction of ST products compared to cigarettes, (2) population estimates of tobacco use transition rates from published literature and nationally representative databases, and (3) the CCI Study regarding the likely changes in consumer behavior (i.e., tobacco use transitions rates) with the introduction of the claim. This model structure is similar to the one adopted by Bachand et al. (2013).

Figure 19: Modeling Effect of Adding an MRTP Claim on an Existing Product



Our model estimates the overall impact of market authorization of the proposed modified risk claim for Copenhagen® Snuff on the U.S. population by comparing the survival of hypothetical populations in two scenarios:

- **Base Case Scenario** – This *status quo* scenario takes into consideration the transitions within the male U.S. population under the existing tobacco product use behaviors for cigarettes and MST products. We focus on males who represent ~ 95% of adult MST users, according to the 2014 National Survey on Drug Use and Health [NSDUH (2016)].
- **Modified Case Scenario** – This scenario reflects the most likely future state in which authorization of the proposed claim yields a change in the transitions within this population based on the CCI Study.

We first estimate the number of premature deaths prevented in a single cohort of one million males starting at age 13 years. We applied transition rates (i.e., probabilities of either remaining in the same state or transitioning from one state to another) to propagate the population through the various states over time. We modeled the single cohort of one million males, at 5-year intervals, starting from the age of 13 years to the age of 73 years under both states. We employed a Markov compartmental model to simulate transitions between 29 mutually-exclusive, tobacco-use states.

We then extend the single-cohort model to a time-staggered, multi-cohort model to estimate the number of premature deaths prevented in a representative, U.S. native-born male population. We utilize this time-staggered, multi-cohort approach to represent a heterogeneous population that estimates the survival of the native-born, U.S. male population by starting a new cohort, with ages from 0 to 4 years, every five years until the population is comprised of ages from 0 to 84 years.

The Base Case is composed of different tobacco use states (nonuser of tobacco products, cigarette smokers, former cigarette smokers, ST users, former ST users, dual users, and former dual users). The transition rates between these states as they exist today are determined from national databases or peer-reviewed literature, (e.g., (Tam, Day, Rostron, & Apelberg, 2015) and (Anderson, Burns, Dodd, & Feuer, 2012)). The unique feature of our model is that we consider the tobacco use behaviors as they exist today and given the long history of use of ST products we were able to use transition probabilities that are well established and based on real-world evidence.

The Modified Case considers the most likely outcome upon FDA authorization of the proposed claim. We use an excess relative risk ratio (ERRR) of 0.09 for current ST users relative to current smokers, based on the all-cause mortality hazard ratio estimates from the Linked Mortality Analyses (MRTPA, Section 7.4.1). To understand the impact of the claim, we focused on seven transitions (Table 7) because they represent behaviors most likely to be impacted by an authorized modified risk claim.

The transition rates in the Modified Case were obtained by adjusting the Base Case transition rates. We used data from the CCI Study to estimate the most likely transition probabilities for five of the transitions based on the percent difference between the likelihood of using Copenhagen[®] Snuff under the Test condition (with claim) relative to the Control (without claim) condition. We assigned conservative theoretical transition rates to two of the transitions because the behaviors are nearly impossible to assess in a premarket setting. These include never tobacco users, who would have started smoking cigarettes, but instead, start using ST products and cigarette smokers who would have quit smoking cigarettes, but instead, switch to ST products.

To determine the benefit of an authorized claim, we estimate the difference in mortality between the two scenarios, representing the number of premature deaths prevented. Our model predicts a reduction in overall mortality in the U.S. population over the next 60 years with an authorized claim, resulting in approximately 93,000 premature deaths prevented upon market authorization of the modified risk claim.

Table 7: Behaviors Most Likely to be Impacted by Authorized Modified Risk Claim

Tobacco Use Transitions
Never User → ST
Former ST Users → ST
Current Smoker → ST
Current Smoker → Dual User (ST + cigarettes)
Dual User → ST
Would-be smoker → ST
Current Smoker Planning to Quit → ST instead of quitting

As with any computational model, our model is based on certain assumptions and limitations. For example, we assume that the transition rates will be static over the prediction period of 60 years. It is difficult, if not impossible, to identify the factors driving tobacco marketplace dynamics, such as the likelihood of potential changes in tobacco regulatory policies and the availability of other FDA authorized, reduced-risk products. We plan to recalculate and update the model estimates periodically based on findings from our postmarket surveillance.

To confirm the robustness of our findings, we conducted numerous sensitivity analyses by varying one to two transition rates at a time over a wide range. [Figure 20](#) illustrates one of these analyses. The black dot represents the population benefit or specifically, the premature deaths prevented following authorization of the claim.

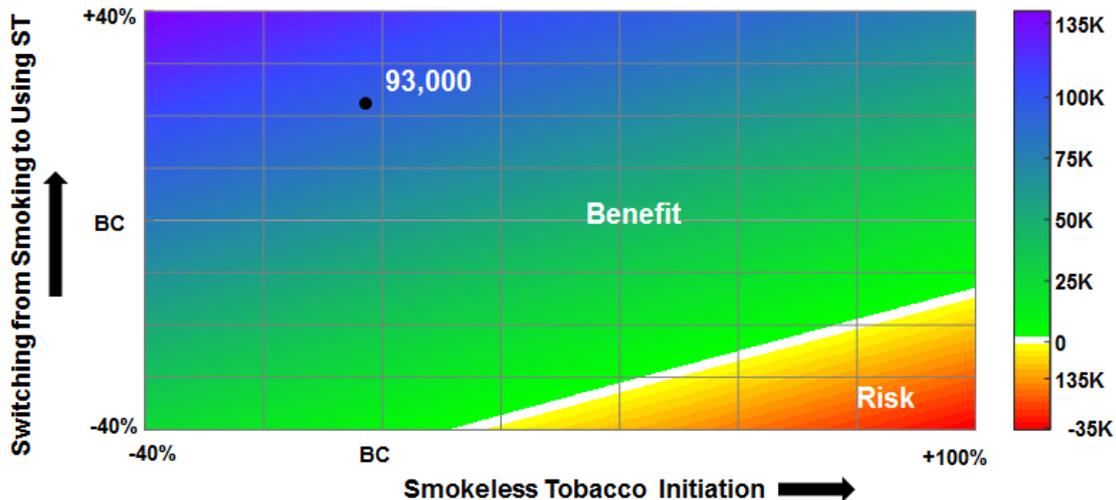
In this sensitivity analysis, we varied two key transition rates over a wide range. The first, along the horizontal x-axis, is never tobacco users who initiate with smokeless tobacco. Increasing the transition rate for initiation would negatively impact population health. The second, along the vertical y-axis, is cigarette smokers who completely switch to smokeless tobacco. Increasing the transition rate for switching would benefit population health.

The label BC represents the base case, which is the “world as is today” scenario.

We varied the initiation rate from -40% to an extreme value of +100%, and we varied the switching rate by +/- 40%.

As shown by the red area labeled risk, these rates would have to move to relatively extreme levels to offset the net benefit.

Figure 20: Net Benefit to the Population: Base Case Compared to Modified Case



d. Conclusions – Estimating the Impact on the Population as a Whole

We developed our model using well-established best modeling practices and tested it using uncertainty and sensitivity analyses. The model indicates that FDA authorization of the proposed modified risk claim yields a modest net health benefit to the population as a whole. Further, model estimates do not indicate unintended consequences that negate this benefit.

V. POSTMARKET SURVEILLANCE

Our postmarket surveillance program will include both active and passive surveillance methods. We plan to conduct appropriate postmarket studies, including cross-sectional and cohort studies, to evaluate the impact of the proposed modified risk claim on product use behaviors and how users perceive the health risks of the product. Additionally, we will use real-world data collected from our postmarket surveillance studies to refine the input parameters of our population model, ensuring the model remains robust and current.

We will prepare reports on adverse events associated with the use of, or exposure to, Copenhagen® Snuff collected from multiple internal and external sources. Those adverse event reports will be provided to FDA periodically. Additionally, we will perform comprehensive literature reviews to gather information on health effects, risk perceptions, patterns of use, and misuse of Copenhagen® Snuff. Finally, we will monitor and analyze data collected in national surveys such as the PATH survey, the National Health Interview study, and the National Youth Tobacco Survey. Specifically, we will monitor changes to and trends about tobacco consumption, risk perceptions, and self-reported health measures at a population level over time.

VI. OVERALL CONCLUSION

The scientific evidence presented in our MRTPA satisfies the statutory requirements for a risk modification order. We have shown that:

- Copenhagen[®] Snuff is significantly less harmful than cigarettes;
- the proposed claim is accurate, non-misleading, and supported by the scientific evidence; and
- a net benefit to the health of the population as a whole is expected upon market authorization of the proposed claim.

USSTC has marketed Copenhagen[®] Snuff for many decades, and decades of epidemiological evidence from U.S. populations establish its harm reduction potential. This epidemiological evidence is extensive, compelling, and undeniable: Switching completely to Copenhagen[®] Snuff from cigarettes, while not risk-free, will reduce the risk of lung cancer.

Although this evidence is clear, it is equally clear that adult tobacco users are uninformed – in fact, *misinformed* – about the relative health risks of Copenhagen[®] Snuff compared to cigarettes. Many adult tobacco users believe that Copenhagen[®] Snuff and other ST products are equally harmful to cigarettes, or even more harmful. These preexisting misperceptions could pose a barrier to our goal of encouraging adult smokers, including dual users, to switch exclusively to Copenhagen[®] Snuff. In our study, a single exposure to an advertisement containing accurate information about the relative health risks of Copenhagen[®] Snuff and cigarettes was not enough to overcome these misperceptions. Perhaps that should not be surprising – not only because these misperceptions are so deeply entrenched, but because consumers are inherently skeptical of advertising claims, and possibly even more skeptical when provided by a tobacco company.

Even so, providing adult smokers with accurate, non-misleading information about the relative lung cancer risk of Copenhagen[®] Snuff and cigarettes is an important first step towards tobacco harm reduction. Although immediate changes in beliefs or behaviors seem unlikely, they are neither required by the statute nor necessary to benefit public health. The proposed claim provides adult smokers with information they need to make informed decisions. Over time, and with repeated exposure, this information will help them better understand the relative risks of Copenhagen[®] Snuff and cigarettes, particularly if it is reinforced by consistent information from credible public health authorities. As observed by (Weaver et al., 2017), tobacco consumers trust federal agencies like FDA and CDC more than the tobacco industry. This, in turn, will encourage complete switching to Copenhagen[®] Snuff, to the benefit of individual smokers and the public health.

We have addressed the key areas of investigation recommended by FDA to determine that our MRTPA meets the standard set forth in Section 911 for modified risk tobacco products.

a. Scientific Substantiation of the Modified Risk Claim and Health Risks of the Tobacco Product

- Using Copenhagen[®] Snuff significantly reduces mortality risk compared to cigarette smoking, particularly for lung cancer and all-cause mortality.
- Switching completely from cigarettes to Copenhagen[®] Snuff reduces risk of lung cancer, supporting the scientific validity of our proposed claim.
- While not risk free, Copenhagen[®] Snuff presents significantly lower disease risks compared to cigarettes.

b. Potential Benefits to the Population as a Whole

i. Effect of Marketing on Consumer Understanding and Perceptions

- Adult tobacco users and nonuser (including LA-24 year olds) understand and do not misinterpret the advertising and labeling with the proposed modified risk claim.
- Adult tobacco users and nonuser continue to believe that Copenhagen[®] Snuff use poses risk to health and that using NRTs, quitting all tobacco use, or never using tobacco products is a less risky choice.
- The proposed claim had little effect on risk perceptions. Our consumer study also found participants failed to recognize the substantial risk difference between ST and cigarettes, which proved consistent with literature findings.

ii. Effect on Tobacco Use Behavior Among Current Users

- Overall, we expect a minimal impact on tobacco use behavior among current users upon market authorization of the proposed modified risk claim. The target audience for our proposed claim, adult smokers not planning to quit, particularly adult males, provides the greatest potential for behavior change.
- We anticipate that the emphasis on “complete switching” and prolonged exposure to marketing information containing the proposed claim will, over time, contribute to understanding of the accurate modified risk claim, adjustment to prior beliefs, and encouragement for ATCs to use Copenhagen[®] Snuff instead of cigarettes.
- Our postmarket surveillance will monitor for potential impacts on tobacco use behavior among current users under real-world conditions
- Copenhagen[®] Snuff has greater abuse potential than, or similar to, that of NRT products but lower than cigarettes based on the pharmacokinetic profile of Copenhagen[®] Snuff and subjective effects measured in our study as well as the published literature.

iii. Effect on Tobacco Use Behavior Among Nonuser

- Former and never users of tobacco products, including young adult (LA-24 year old) nonuser, have minimal intent to use Copenhagen[®] Snuff, which does not change after reviewing the proposed claim.
- There is low likelihood that Copenhagen[®] Snuff will have an unintended effect of increasing youth initiation of the product beyond the current rates observed for the category or change the factors influencing youth ST use.
- We have no evidence that nonuser would adopt Copenhagen[®] Snuff when marketed with the proposed claim and switch to more harmful tobacco products. The literature reports regarding association between ST use and cigarette smoking are conflicting and do not establish a causal relationship.
- Direct evidence regarding nonuser adopting Copenhagen[®] Snuff and switching to cigarettes can only be obtained after authorization of the proposed claim by FDA, which will be assessed during postmarket surveillance (Section 8.1).

iv. Estimate of Impact on the Population as a Whole

Our model, developed using well-established best modeling practices and tested using uncertainty and sensitivity analyses, indicates that authorization of a modified risk claim yields a modest net population health benefit. The model estimates do not indicate any unintended consequences that negate this benefit.

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