

2.3.: EXECUTIVE SUMMARY

TABLE OF CONTENTS

2.3.	OVERVIEW	5
2.3.1.	Background.....	10
2.3.1.1.	The harm caused by tobacco use is primarily attributable to cigarette smoking.....	10
2.3.1.2.	ST products are substantially less harmful than cigarette smoking.....	10
2.3.1.3.	The proposed modified risk claim presents a harm reduction opportunity for Adult Smokers.	14
2.3.2.	Scientific Evidence Supporting Market Authorization.....	15
2.3.3.	Health Risks of the Tobacco Product	17
2.3.3.1.	Epidemiological evidence on the Health Risks of ST applies to the candidate product.	18
2.3.3.2.	MST as the Predominant Form of ST Use.....	19
2.3.3.3.	Candidate Product and USSTC Contribution to Total MST Volume	19
2.3.3.4.	Tobacco and Manufacturing Considerations for the Candidate Product.....	20
2.3.3.5.	Summarizing the totality of the health risk evidence supporting this MRTPA.....	23
2.3.3.5.1.	Switching to the candidate product from cigarettes reduces lung cancer risk.....	24
2.3.3.5.2.	ST use presents substantially lower all-cause mortality risk than cigarette smoking.....	27
2.3.3.5.3.	ST use presents substantially lower mortality risks for all cancers than cigarette smoking.....	28
2.3.3.6.	Conclusions – Scientific Health Risk Evidence Supporting Market Authorization	28
2.3.4.	Effect of Marketing on Consumer Understanding and Perceptions	29
2.3.4.1.	Consumers understand the proposed advertising and labeling and are not misled to believe the candidate product is without risk.....	31
2.3.4.2.	The proposed modified risk claim did not alter risk perceptions.	34
2.3.4.2.1.	Perceived Absolute Risk of the Candidate Product.....	34
2.3.4.2.2.	Perceived Risk of the Candidate Product Relative to Cigarettes and Other ST Products	34

2.3.4.3.	Conclusions – Effect of Marketing on Consumer Understanding and Perceptions.....	35
2.3.5.	Effect on Tobacco Use Behavior among Current Users.....	35
2.3.5.1.	We expect low likelihood that current tobacco product users will begin to use the candidate product upon market authorization of the proposed modified risk claim.	36
2.3.5.2.	We found no statistically significant increase or decrease among ATC with respect to the likelihood of dual use involving the candidate product.	39
2.3.5.3.	There is little likelihood that ATC who adopt the candidate product will switch to or switch back to other tobacco products that present higher levels of individual health risk.	39
2.3.5.4.	We observed no statistically significant increase or decrease in the likelihood that users who may have otherwise quit using tobacco products will instead use the candidate product.....	40
2.3.5.5.	Actual use behavior for the candidate product is well established, stable, and not likely to change.....	40
2.3.5.6.	The candidate product exhibits greater than, or similar, abuse potential to NRT gum, but lower abuse potential than cigarettes.....	41
2.3.5.7.	Conclusions – Effect on Tobacco Use Behavior among Current Users	42
2.3.6.	Effect on Tobacco Use Behavior among Non-users.....	43
2.3.6.1.	We expect no increase or decrease in the likelihood of initiation of candidate product use in adult non-users (never and former users), LA-24 non-users and youth.	43
2.3.6.2.	We expect no increase or decrease in the likelihood that non-users who may adopt the candidate product will switch to other tobacco products that present higher levels of individual health risks (i.e. cigarettes).	46
2.3.6.3.	There is no evidence that former users of tobacco products will reinitiate use with the candidate product.	47
2.3.6.4.	Conclusions – Effect on Tobacco Use Behavior among Non-users.....	47
2.3.7.	Effect on the Population as a Whole.....	48
2.3.7.1.	Framework and Applications of the ALCS Cohort Model.....	48
2.3.7.2.	Results of the ALCS Cohort Model.....	53
2.3.7.3.	ALCS Cohort Model Assumptions and Limitations	53
2.3.7.4.	Conclusions – Effect on the Population as a Whole.....	53
2.3.8.	Overall Conclusion	53
2.3.8.1.	Health Risks of the Tobacco Product	54

2.3.8.2.	Effect of Marketing on Consumer Understanding and Perceptions	55
2.3.8.3.	Effect on Tobacco Use Behavior among Current Users.....	55
2.3.8.4.	Effect on Tobacco Use Behavior among Non-users.....	55
2.3.8.5.	Effect on the Population as a Whole.....	56
2.3.9.	Literature Cited.....	56

LIST OF TABLES

Table 2.3-1:	Perceived Harm and Risk Misperceptions.....	13
Table 2.3-2:	Tabulated Index of Research Studies and Data	16
Table 2.3-3:	Claims Comprehension and Intentions Study Sample Size and Study Subgroups	30
Table 2.3-4:	Composite Scores (unadjusted means) of Responses Related to Candidate Product Trial, Use or Switching among Current Tobacco Users	37
Table 2.3-5:	Proportion of Current Tobacco Users Indicating Positive Affect	38
Table 2.3-6:	Average Composite Scores for Intention to Try and Use the Candidate Product among Adult Non-users	43
Table 2.3-7:	Proportion of Adult Non-users Indicating Positive Affect	44

LIST OF FIGURES

Figure 2.3-1:	Distribution of Adult Tobacco Consumers in 2014 Based on PATH (Wave 1)	7
Figure 2.3-2:	Proportion of Adult Tobacco Consumers that Believe that ST is Less Harmful than Cigarettes.....	8
Figure 2.3-3:	Advertising with the Proposed Modified Risk Claim	9
Figure 2.3-4:	Harm Perceptions among Adult Cigarette Smokers – PATH Wave 1 (2013-2014)*	12
Figure 2.3-5:	Interest in reduced-risk tobacco products among established smokers – PATH WAVE 1 2014.....	15
Figure 2.3-6:	USSTC Volume within MST and Chewing Tobacco Category (1972- 2011) and Study Periods of Prospective Studies of the Health Effects of ST Products	19
Figure 2.3-7:	Contribution of Copenhagen Fine Cut Snuff to USSTC’s Market Share, 1985-2016.....	20

Figure 2.3-8: Average TSNA levels (ppm, dry weight basis) in commercial moist smokeless tobacco products A, B, and C 1997–2010.....	22
Figure 2.3.9: Hierarchy of Evidence	24
Figure 2.3-10: Cumulative Risk of Lung Cancer Mortality among Men According to the Age When They Stop Smoking	25
Figure 2.3-11: Mortality Hazard Ratios ^a from Neoplasms of the Trachea, Bronchus, and Lung: Adjusted Hazard Ratio Estimates for Various Tobacco Use Practices Compared to Never-Tobacco Users	26
Figure 2.3-12: All-Cause Mortality Hazard Ratios ^a in ST users and Smokers Compared to Never Users	27
Figure 2.3-13: Mortality Hazard Ratios from Malignant Neoplasms in ST users and Smokers Compared to Never Users.....	28
Figure 2.3-14: Proposed Modified Risk Claim Comprehension.....	31
Figure 2.3-15: General Harm Associated with the Candidate Product Pre-Post for Test and Control	33
Figure 2.3-16: Nicotine Pharmacokinetic Profile for Copenhagen® Snuff Relative to Own Brand Cigarettes and Nicotine Polacrilex Gum.....	42
Figure 2.3-17: Past Month Smokeless Tobacco Use Among People Aged 12 Years or Older, by Age Group: Percentages, 2002-2016.....	45
Figure 2.3-18: Modeling Effect of Adding an MRTTP Claim on an Existing Product	49
Figure 2.3-19: Mean Difference in Number of Survivors Between the Master and Base Case Scenarios: Point Estimates and Credible Intervals	52

2.3. OVERVIEW

Altria Client Services LLC (“ALCS”) on behalf of U.S. Smokeless Tobacco Company LLC (“USSTC”)¹ submits this Modified Risk Tobacco Product Application (MRTPA) to market Copenhagen[®] Snuff Fine Cut (candidate product) with the following proposed modified risk claim:

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

The candidate product is a grandfathered product (FDA Grandfather Status # GF1200194), commercially marketed in the U.S. as of February 15, 2007. Because it is not a new tobacco product as defined by FDCA Section 910(a)(1), it does not require premarket review and authorization.²

We seek a risk modification order under Section 911(g)(1) of the Federal Food, Drug and Cosmetic Act (FDCA), which requires FDA to authorize a proposed modified risk claim when a candidate 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”.

The scientific evidence presented in this MRTPA satisfies the statutory requirements for a proposed modified risk order. We demonstrate that:

1. the candidate product is significantly less harmful than cigarettes;
2. the proposed modified risk claim is accurate, non-misleading, and supported by the scientific evidence; and
3. a net benefit to the health of the population as a whole is expected upon market authorization of the proposed modified risk claim.

Having met these requirements, we respectfully request that FDA carry out its statutory responsibility to authorize the proposed claim.

USSTC has marketed the candidate product for many decades. As a result, substantial epidemiological evidence exists regarding disease risks of the candidate product in the U.S.

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[®] Fine Cut and variants thereof have been on the market since 1822. Since 2007, USSTC has made minor modifications to Copenhagen[®] Snuff Fine Cut, which are the subject of a separate pending Substantial Equivalence review. The candidate product subject to the MRTPA is the product for which FDA granted grandfathered status (Grandfather Number – GF1200194) on November 1, 2012 ([Appendix 2.3-1](#)).

population. This evidence is extensive, compelling, and undeniable: Switching completely to the candidate product from cigarettes, while not risk-free, will reduce the risk of lung cancer.

Paradoxically, it is also undeniable that adult tobacco users 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 adult tobacco users erroneously believe that the candidate product and other ST products are equally harmful to cigarettes or even more harmful. Providing adult smokers with accurate, non-misleading information about the relative lung cancer risk of the candidate product compared to cigarettes is an important first step towards tobacco harm reduction.

A harm reduction strategy that informs adult smokers about reduced risk products, subject to FDA oversight, will *complement*, not *compete*, with proven prevention and cessation strategies. This approach should focus on reducing tobacco-related morbidity and mortality among the population of adults who continue to use tobacco products by empowering them to make an informed decision to choose a product proven to be lower on the continuum of tobacco product health risk.

USSTC is committed not only to making such products available to consumers, but also to pursuing FDA authorization to provide consumers with accurate and non-misleading information about their lower health risks. Without this information, the ability of adult tobacco consumers to make informed decisions will continue to be unjustifiably constrained. Accordingly, USSTC seeks authorization to communicate a modified risk claim informing adult cigarette smokers that switching completely to the candidate product from cigarettes reduces risk of lung cancer.

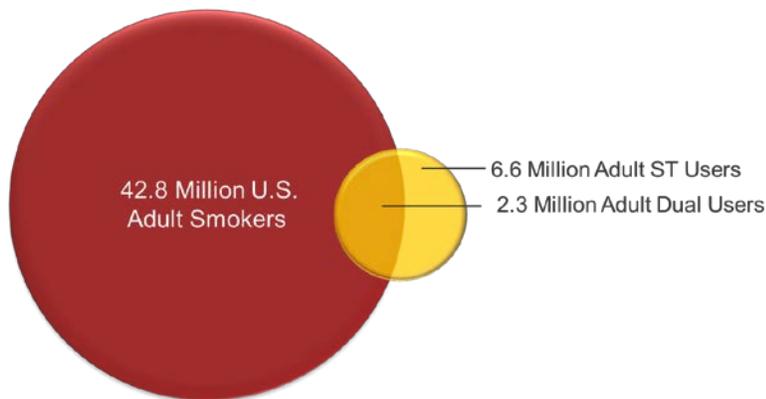
For many years, and in numerous public comments submitted to FDA, we have emphasized that adult consumers are *entitled* to accurate and non-misleading information about tobacco products – as a matter of both sound policy and law. This principle applies irrespective of FDCA §911(g)(1)(B), which purports to require 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.” We believe this requirement is unconstitutional: an impermissible encroachment on the First Amendment. The U.S. Supreme Court has long “rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information.” *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002) ([Appendix 2.3-3](#)). The proposed claim provides adult smokers with accurate and non-misleading information that they need to make informed decisions. The First Amendment guarantees both the right of adult smokers to receive that information and the right of manufacturers to provide it. Nevertheless, we demonstrate that we satisfy the “population effects” requirement with evidence summarized in this Section.

The candidate product is a non-combustible tobacco product, low on the continuum of risk. As part of the July 2017 announcement, Dr. Scott Gottlieb, FDA Commissioner, acknowledged 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.³ 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 smokeless tobacco (ST) products (including the candidate product and similar moist smokeless tobacco (MST) products) demonstrates that such products present significantly lower harm than cigarettes.

Adult smokers who are unwilling or unable to quit smoking should be encouraged to switch to a less harmful product, like the candidate product. 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 (~2.3 million, [Figure 2.3-1](#)) of adult ST consumers who continue to smoke. Dual users present a significant 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.⁴

Figure 2.3-1: Distribution of Adult Tobacco Consumers in 2014 Based on PATH (Wave 1)



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

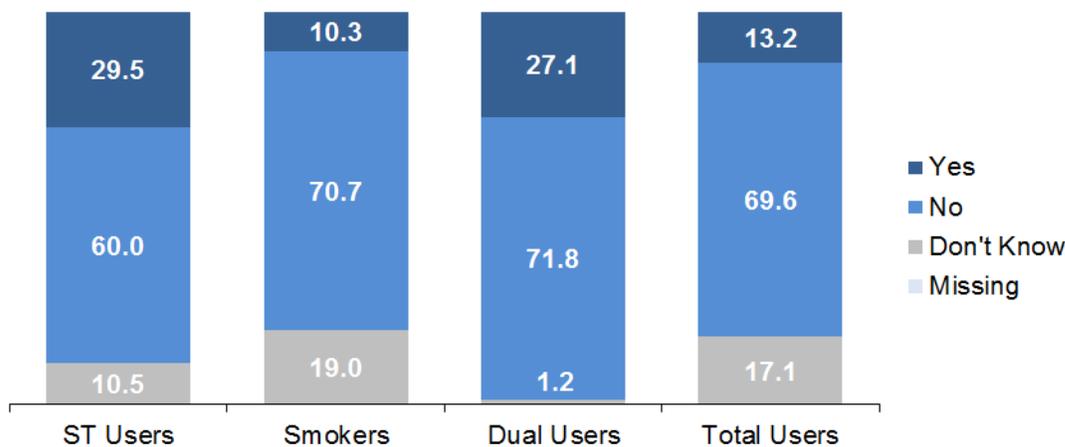
Definitions: Cigarette smokers include those who report having smoked at least 100 cigarettes in their lifetime and now smoke every day or some days. Smokeless Tobacco (ST) users include those who report having used ST at least 20 times in their lifetime and now using ST every day or some days. Dual 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.

³ July 28, 2017 – “Protecting American Families: Comprehensive Approach to Nicotine and Tobacco.” Scott Gottlieb, M.D., Commissioner, White Oak Campus, Silver Spring, MD

⁴ 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 adult tobacco consumers wrongly believe that ST products are as harmful as cigarettes, or even more harmful. For example, in the PATH (Population Assessment of Tobacco and Health) WAVE 1 survey, the vast majority of smokers (more than 90%) said that ST is as or more harmful than cigarettes.⁵ Similar findings are evident in the HINTS (Health Information National Trends) survey (Figure 2.3-2) where a vast majority of smokers (71%) and dual users (72%) did not believe that ST is less harmful than cigarettes. Numerous published studies corroborate these findings (as shown in Table 2.3-1).

Figure 2.3-2: Proportion of Adult Tobacco Consumers that Believe that 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?” (Appendix 2.3-4)

‘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.

Correcting misperceptions about the relative risk of cigarettes and ST products 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 (Figure 2.3-3). We focus on

⁵ 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.

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 2.3-3: Advertising with the Proposed Modified Risk Claim



Our application includes the following scientific evidence, reviewed in this Executive Summary and described more fully in this MRPTA:

- Published epidemiology and our analyses of two nationally representative public health surveys ([Appendix 7.4.1-3](#)) linked to the National Death Index clearly show that completely switching from cigarettes to ST products, like the candidate product, presents lower risk of lung cancer and that ST products present lower overall health risks than cigarettes. The candidate product 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 the candidate product and to establish that complete switching to the candidate product from smoking will similarly result in a lower risk of lung cancer.
- Our consumer study ([Appendix 7.3.2-1](#)) shows that the proposed claim is understood and not misleading.
- Our consumer study also shows that former and never tobacco users do not express intent to use the candidate product after reviewing the proposed modified risk claim.
- Our clinical study ([Appendix 7.3.1-1](#)) demonstrates that the candidate product exhibits relatively lower abuse potential than cigarettes.

Our ALCS Cohort Model indicates a net population health benefit if the candidate product is marketed with the proposed claim. Based on the scientific evidence, we have satisfied all of the applicable statutory requirements needed for FDA authorization of the proposed modified risk claim.

2.3.1. Background

2.3.1.1. 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. 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) was 18.1%, according to SEER data from the National Cancer Institute.⁶ Smoking is directly responsible for more than 80% of lung cancer [Surgeon General Report (2004)].

Quitting tobacco use is the most effective means of reducing the risk of tobacco-related disease for smokers. For those who do not quit all tobacco, completely switching from cigarettes to demonstrably less hazardous ST products can reduce the risk of lung cancer and other serious diseases.

2.3.1.2. ST products are substantially less harmful than cigarette smoking.

The candidate product is not safe. The U.S. Surgeon General and other public health authorities have determined that ST products are addictive and can cause serious diseases, some of which are addressed by the federally mandated warnings.

The overwhelming scientific, medical, and public health consensus, however, confirms that MST products, including those widely available in the U.S., are substantially less hazardous than cigarettes (Hatsukami et al., 2007; Zeller & Hatsukami, 2009). This consensus is based on extensive and compelling scientific evidence, including epidemiological disease risk data in human populations from the U.S. (Section 2.3.3).

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

“[T]he consumption of non-combustible tobacco is of the order of 10-1,000 times less hazardous than smoking, depending on the product.”⁷

⁶ 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).

⁷ Tobacco Advisory Group, Royal College of Physicians of London, *Protecting Smokers, Saving Lives* (London RCP 2002).

“[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.”⁸

“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.”⁹

“Studies have consistently reported that cigarette smoking significantly increases the risk of LC. Most studies reported that ST users do not have an increased risk of LC compared with non-smokers.”¹⁰

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.”¹¹

“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.”¹²

More recently, when announcing FDA’s comprehensive policy for nicotine and tobacco,¹³ Dr. Scott Gottlieb, FDA Commissioner, remarked:

“[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.”

“In a world where there is no mandated reduction in the levels of nicotine in noncombustible products, our compliance policies should account for changes that

⁸ WHO Study Group on Tobacco Product Regulation (TobReg), *The Scientific Basis of Tobacco Product Regulation*, 951 WHO Technical Reports Series (2008).

⁹ 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).

¹⁰ 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

¹¹ M. Zeller et al., *supra* note (Zeller & Hatsukami, 2009).

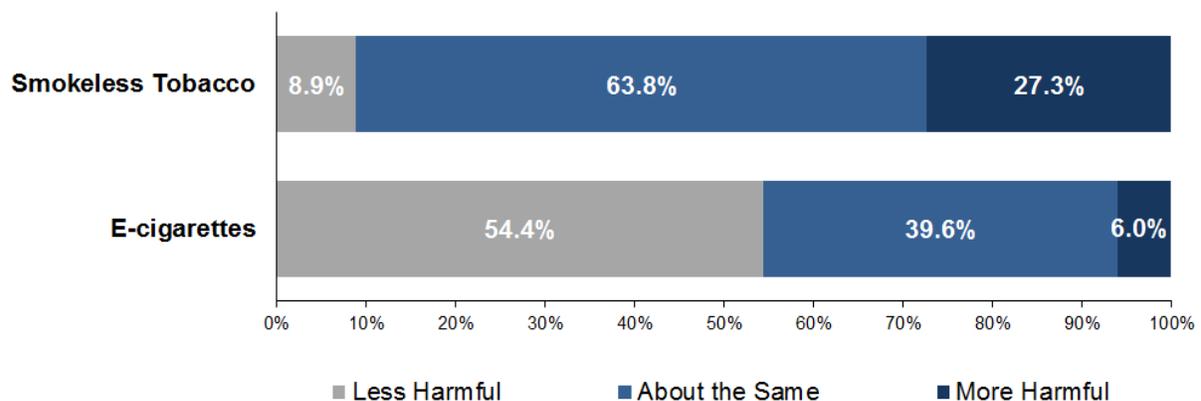
¹² *Id.* at 327.

¹³ Remarks made by Scott Gottlieb, M.D., Commissioner, White Oak Campus, Silver Spring, MD on July 28, 2017 - Protecting American Families: Comprehensive Approach to Nicotine and Tobacco Scott Gottlieb, M.D., Commissioner, White Oak Campus, Silver Spring, MD. Accessed at <https://www.fda.gov/NewsEvents/Speeches/ucm569024.htm>

will move addicted smokers down that continuum of risk to these less harmful products.”

Adult smokers are uninformed – in fact, *misinformed* – of the scientific fact that ST products are substantially less harmful than cigarette smoking. The ongoing PATH survey sponsored by FDA underscores the prevailing misperception among adult smokers, revealing that the vast majority of adult smokers – more than 90% – believe that ST is as or more harmful than cigarettes (Figure 2.3-4).

Figure 2.3-4: Harm Perceptions among Adult Cigarette Smokers – PATH Wave 1 (2013-2014)*



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

* Harmfulness of using [product] compared to smoking cigarettes (among every day or some days adult tobacco users). In PATH, “Don’t Know” is not included in the valid response set. Percentages may not sum to 100% due to rounding. Data for E-cigarettes included to provide context.

The HINTS survey (Figure 2.3-2) showed similar results among tobacco users. Even ST users (60%) and Dual Users of ST and cigarettes (72%) did not perceive ST as less harmful than cigarettes.

Published studies confirm the results of ALCS’ analyses of PATH (Appendix 3.2-1) and HINTS (Appendix 2.3-4) data. In a 2005 survey of more than 2,000 adult U.S. smokers, only 10.7 percent correctly agreed that ST products are less hazardous than cigarettes, while 82.9 percent disagreed and 6.4 percent 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*".¹⁴

Table 2.3-1 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.

Table 2.3-1: 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 are any ST that 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

¹⁴ *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).

Authors (Date)	Findings Related to Risk Perceptions of ST	Percent Risk Misperception¹
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)

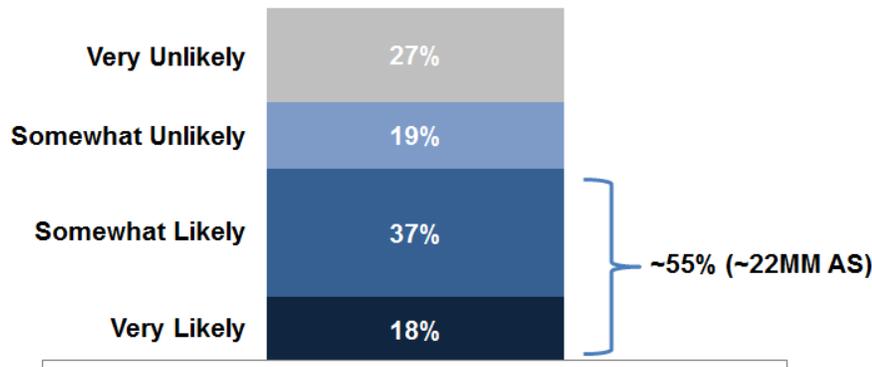
¹ Misperception means belief that ST is equally or more harmful than cigarettes.

Taken together, these studies demonstrate that between 40 and 93 percent of 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.

2.3.1.3. 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 (~22MM, 55%) are interested in and likely to use reduced-risk products marketed with a reduced risk claim (Figure 2.3-5).

Figure 2.3-5: Interest in reduced-risk tobacco products among established smokers – PATH WAVE 1 2014



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?”

The candidate product, marketed with an FDA-authorized modified risk claim, will provide a reduced-risk alternative for adult smokers, particularly dual users of cigarettes and ST. 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, generally, and dual users, particularly, better understand the relative risks of the candidate product and cigarettes and encourage them to switch completely to the candidate product. We verified this claim to be:

- relevant to smokers;
- clear and believable;
- understood and not misleading to adult smokers Section 2.3.4; and
- substantiated by robust scientific evidence (Section 2.3.3).

2.3.2. Scientific Evidence Supporting Market Authorization

The evidence provided in this MRTPA satisfies the statutory content requirements set forth in FDCA §911(d). Specifically this MRTPA includes:

1. a description of the proposed product and the proposed advertising and labeling (Section 3.1 and Section 4.1, respectively);
2. the conditions for using the product (Section 3.2);
3. the formulation of the product (Section 3.1);
4. sample product labels and labeling (Section 4.1);

5. all documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the product to reduce risk or exposure and relating to human health (Section 7); and
6. data and information on how consumers actually use the tobacco product (Section 3.2).

The statute compels FDA to authorize the proposed modified risk claim if the Agency finds that the information included in our MRTPA sufficiently demonstrates that smokers switching completely to the candidate product will significantly reduce the harm and risk of lung cancer to individual tobacco users and benefit the health of the population as a whole.

In its March 2012 Draft MRTPA Guidance, FDA identified five key areas of investigation to determine if a MRTPA meets this standard.

1. Health Risks of the Tobacco Product
2. Effect of Marketing on Consumer Understanding and Perceptions
3. Effect on Tobacco Use Behavior among Current Users
4. Effect on Tobacco Use Behavior among Non-users
5. Effect on the Population as a Whole.

Our MRTPA presents scientific evidence on these five key areas of investigation, including individual health risks and potential population effects. In Sections 6.1 through 6.5, we summarize research findings related to these topics. Table 2.3-2 provides an index of studies and data included in Section 7, which support this application. Below we summarize our major findings.

Table 2.3-2: Tabulated Index of Research Studies and Data

Area	Study type	Title	Section
Health Risks of the Tobacco Product: Section 911(g)(4)(A) Key Findings Summarized in Section 6.1	Secondary Analysis	Health Risks - Literature Summary	7.5.6-1 and 7.5.6-2
	Secondary Analysis	Smokeless Tobacco Mortality Risks: Analyses of Two Contemporary Nationally Representative Longitudinal Mortality Studies	7.4.1
	Chemical Analysis	HPHC Levels in Copenhagen® Snuff Fine Cut	7.1
Effect of Marketing on Consumer Understanding and Perceptions: Section 911(h)(1) Key Findings Summarized in Section 6.2	Secondary analysis	Perceptions – Literature Summary	7.5.7-1 and 7.5.7-2
	Adult Human Studies	Qualitative Study to Support Claims Language Development for Moist Smokeless Tobacco (CS01 Claims Qualitative Study)	7.3.3
	Adult Human Studies	Qualitative Study to Explore Modified Risk Communications Bundles for Moist Smokeless Tobacco (CS01.1 Claims Qualitative Study)	7.3.3

Area	Study type	Title	Section
	Adult Human Studies	ALCS-CMI-17-20-MST - Claim Comprehension and Intentions Study for Product Currently Marketed as Copenhagen® Snuff (CCI Study)	7.3.2
Effect on Tobacco Use Behavior among Current Tobacco Users Key Findings Summarized in Section 6.3	Secondary analysis	Behavior – Users Literature Summary	7.5.2-1 and 7.5.2-2
	Adult Human Studies	ALCS-CMI-17-20-MST - Claim Comprehension and Intentions Study for Product Currently Marketed as Copenhagen® Snuff (CCI Study)	7.3.2
	Adult Human Studies	ALCS-RS-17-02-MST – Pharmacokinetic Study with Subjective Effects	7.3.1
Effect on Tobacco Use Behavior among Non-users: Section 911(g)(4)(C) Key Findings Summarized in Section 6.4	Secondary analysis	Behavior – Non-users Literature Summary	7.5.3-1 and 7.5.3-2
	Secondary analysis	National Surveys	3.2
	Adult Human Studies	Qualitative Study to Explore Modified Risk Communications Bundles for Moist Smokeless Tobacco	7.3.3
Effect on the Population as a Whole: Section 911(g)(1)(B) Key Findings Summarized in Section 6.5	Modeling	Population Model Development, Input Parameters, and Outcomes	7.4.2
Postmarket Surveillance Section 911(g)(1)(B) Proposed Program Described in Section 8.1	Adult Human Secondary Analysis	Proposed program of study Adverse Event Summary	8.1 7.4.3

2.3.3. Health Risks of the Tobacco Product

Based on our review of published epidemiology and our analyses of two large, nationally representative data sets from the National Center for Health Statistics with the data from the National Longitudinal Mortality Study (U.S. Census Bureau) (NLMS) and National Health Interview Survey (CDC) (NHIS), 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 the candidate product from cigarettes reduces the risk of lung cancer. The weight and consistency of the evidence substantiates our proposed claim.

2.3.3.1. Epidemiological evidence on the Health Risks of ST applies to the candidate product.

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, the health risks of the candidate product can be sufficiently assessed using existing epidemiology data for U.S. smokeless tobacco products. 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, the candidate product and other USSTC MST products occupied sizeable market shares among the MST products used during the time period of these studies, which means that the epidemiological data reasonably reflects the health effects of the candidate product and other USSTC products. Third, the production process for USSTC MST products, including for the candidate product, 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.

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 (b) (4) 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.

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.

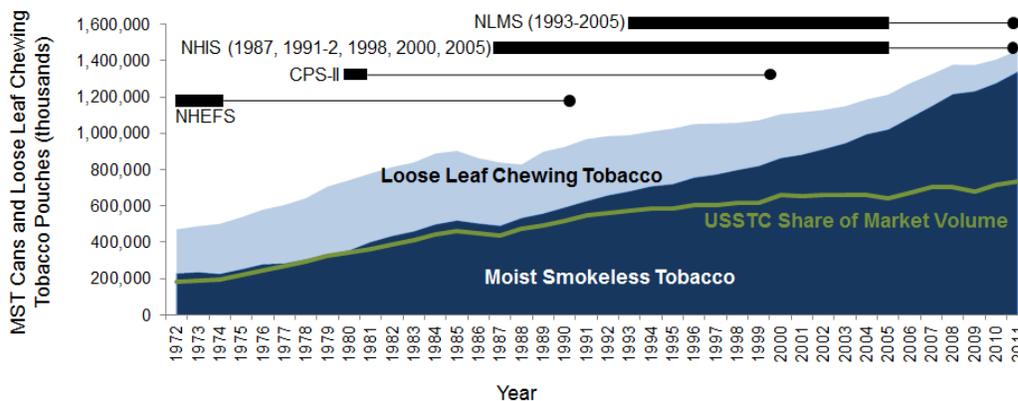
International smokeless product types and usage patterns are quite different from U.S. MST, and the health risk profiles vary widely. In some Southeast Asian countries smokeless tobacco is often combined with betel and areca for chewing (e.g., pan masala, gutka, Manipuri tobacco, mawa, and dohra). Other 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. In Sweden, an MST form commonly called "snus" is almost exclusively used. The epidemiological evidence regarding Swedish Snus demonstrates that these products exhibit a lower health risk profile compared to cigarettes.

Simply put, if epidemiological evidence is ever going to support the granting of any MRTP claim filed in connection with any tobacco product, such evidence will support the granting of this one.

2.3.3.2. MST as the Predominant Form of ST Use

MST products are the predominant form of ST use. Figure 2.3-6 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 2.3-6. 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 2.3-6: USSTC Volume within MST and Chewing Tobacco Category (1972-2011) and Study Periods of Prospective Studies of the Health Effects of ST Products



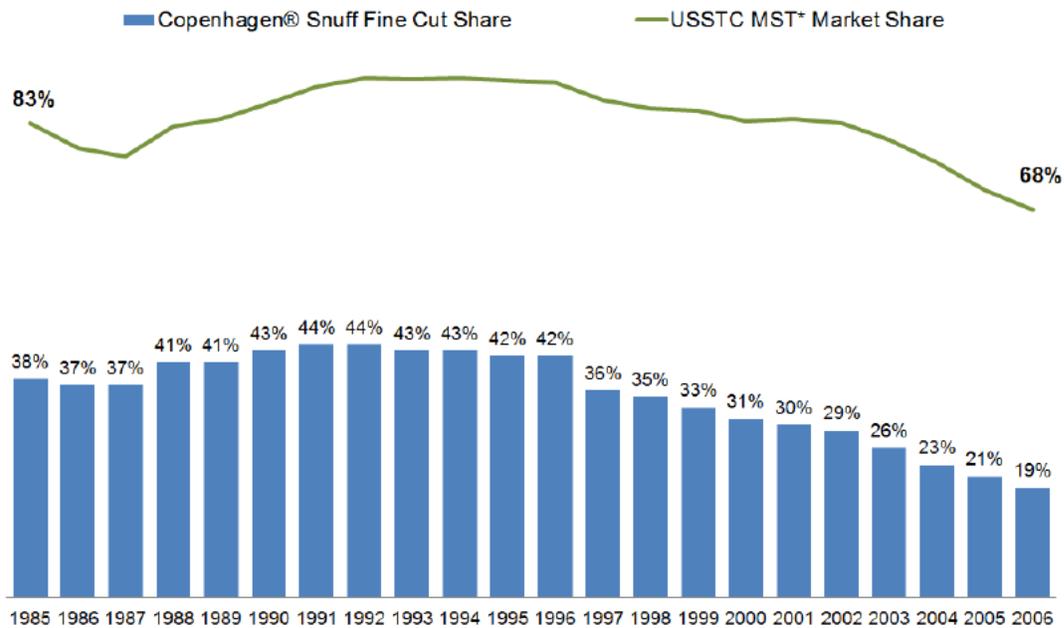
Source: Unit volume of moist smokeless tobacco and loose leaf chewing tobacco derived from Maxwell Reports 1972-2011 and study periods for prospective epidemiological studies of smokeless tobacco. USSTC volumes are based on USSTC historical shipment data (Appendix 2.3-2) and USSTC RAD SVT projected volume 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.

2.3.3.3. Candidate Product and USSTC Contribution to Total MST Volume

Figure 2.3-7 provides market share data for USSTC products and the candidate product 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 the candidate product accounted for 38% of the MST category. Over the time period of the epidemiology studies, the candidate product occupied a sizeable market share among the MST products. For this reason, and the reasons presented above, we conclude that the health risks of the candidate product can be sufficiently assessed using existing epidemiology data for U.S. smokeless tobacco products.

Figure 2.3-7: Contribution of Copenhagen Fine Cut 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).

2.3.3.4. Tobacco and Manufacturing Considerations for the Candidate Product

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 (b) (4) fermentation process for almost 200 years.

This trade secret process was invented in 1822 and can be documented based on historical product formulas for the candidate product to as early as 1905. In brief, this batch process includes addition of water, flavoring ingredients and salts, to a blend of dried, cut tobacco. (

(b) (4)

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. The candidate product, in particular, used tobacco types, blends, and manufacturing processes comparable to all USSTC MST products, throughout the time period of the epidemiology studies. The candidate product, 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 2.3-8. These efforts, which are described below, included: (1) improvements to farming practices; (2) manufacturing process enhancements; and (3) Vertically Integrated Process Management (VIPM).

First, manufacturers and academic researchers collaborated during the 2000s to develop low converter seed varieties to help reduce TSNA formation in tobacco leaf relative to earlier generations of seed varieties. Other efforts to reduce TSNAs at the farm level have focused on fertilizer application rates, barn structure, ventilation, and temperatures associated with the curing process. Since 2005, USSTC has included certain Good Agricultural Practices, including production, harvesting, and curing requirements in its contracts with farmers, to help reduce the formation of TSNAs on the farm.

Second, USSTC implemented 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. (b) (4)



Third, in 2001, USSTC modified its manufacturing process through the VIPM program. Part of the VIPM program involved using production equipment that can be easily sanitized and systematically examining TSNA levels. By 2005, USSTC had achieved its goal of preventing any increase in TSNA from the time we purchased the leaf from farmers through the end of the product's shelf life.

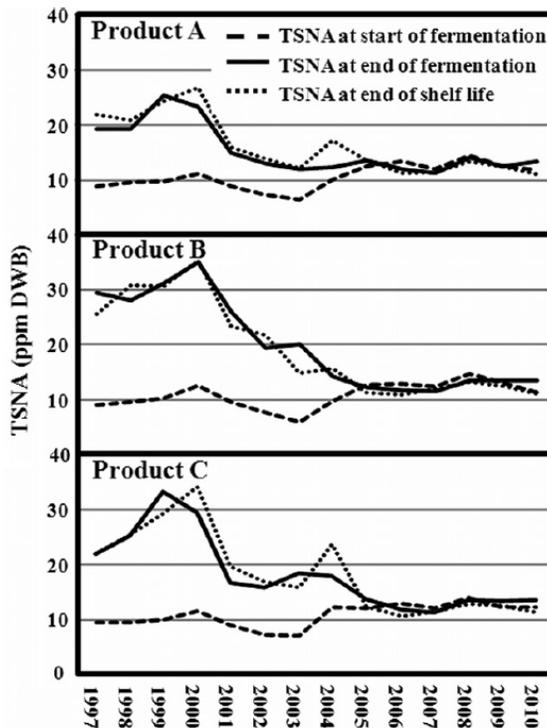
This comprehensive program from the mid-1970s until 2005 sought to address TSNA levels and formation in USSTC products. These efforts substantially reduced TSNA levels in USSTC products. While not completely eliminated, these efforts resulted in substantial TSNA reductions of up to 90% in USSTC's products by the late 1990s.

Djordjevic et al observed general TSNA reductions in the marketplace, reporting that, over the time period of 1980 to 1998, TSNA content was reduced by 70-90% for two "leading

U.S. snuff brands.”¹⁶ We note that during this period the candidate product had approximately 40% of the MST market share. Since full implementation of process refinements by USSTC in 2005, TSNA levels have been consistently about 10 µg/g or lower (Fisher et al 2012), as confirmed by the HPHC testing report (Appendix 7.3.1-3), and are consistently no higher at the end of product retail shelf life than those levels found in tobaccos purchased from farmers.

In short, refinements to USSTC’s moist snuff production process do not make existing epidemiology any less relevant to current USSTC moist snuff products, including the candidate product.

Figure 2.3-8: 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

¹⁶Values are drawn from the published literature for samples that could be reliably identified as USSTC products (Borgerding, Bodnar, Curtin, & Swauger, 2012; Brunnemann, Qi, & Hoffmann, 2002; Brunnemann, Scott, & Hoffmann, 1982; Djordjevic, Brunnemann, & Hoffmann, 1989; Hoffmann & Adams, 1981; Hoffmann, Adams, Lisk, Fisenne, & Brunnemann, 1987; Hoffmann et al., 1995; Hoffmann, Harley, Fisenne, Adams, & Brunnemann, 1986; Richter, Hodge, Stanfill, Zhang, & Watson, 2008), as well as unpublished measurements of USSTC moist snuff products collected by ALCS between 2005 and 2008.

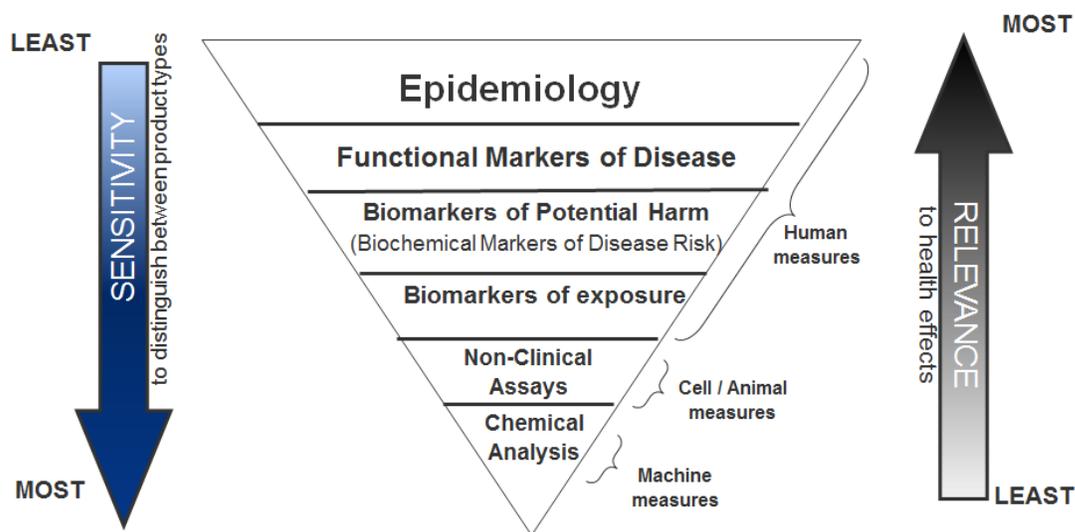
2.3.3.5. Summarizing the totality of the health risk evidence supporting this MRTPA

Section 6.1 discusses the health risk evidence related to the use of ST products in the U.S. compared to cigarette smoking.

We conclude from several converging lines of evidence that ST is less risky than cigarettes and switching completely to the candidate product from cigarettes reduces risk of lung cancer. Within the hierarchy of evidence, we assign significant weight to the epidemiological studies (Figure 2.3.9), 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.

1. Epidemiological evidence provides the ultimate 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.
2. ST is non-combustible. As a result, there is no tar or tobacco smoke and no 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.
3. 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.
4. Animal studies conducted under exaggerated exposure conditions that do not reflect human use level indicate perturbations in biological systems; however, the epidemiological evidence indicates that these changes are not relevant to human disease.
5. 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.
6. 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.

Figure 2.3.9: Hierarchy of Evidence



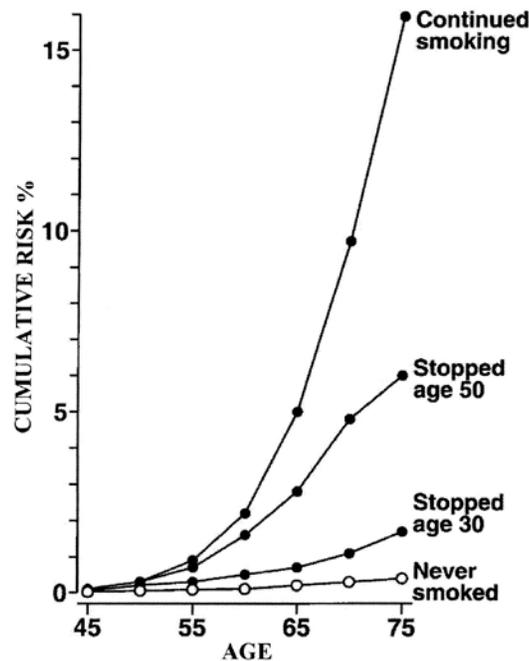
Our analysis of the health risks associated with the candidate product incorporates two sets of epidemiology data comprising the most current risks for U.S. marketed products: the NHIS and NLMS mortality linkages (Section 7.4.1). We also examine published epidemiological evidence related to the use of ST (Section 7.5.6-1 and 7.5.6-2).

Immediately below, we summarize our conclusions based on three lines of evidence: lung cancer risk when switching completely to the candidate product from cigarettes, all-cause mortality of ST compared to cigarettes, and all cancer mortality risk of ST compared to cigarettes.

2.3.3.5.1. Switching to the candidate product from cigarettes reduces lung cancer risk.

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 2.3-10. 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 the candidate product.

Figure 2.3-10: Cumulative Risk of Lung Cancer Mortality among Men According to the Age When They Stop Smoking



Source: (Vineis et al., 2004)

Cigarette smoking has a high risk of lung cancer. 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%, according to recent SEER data).¹⁷

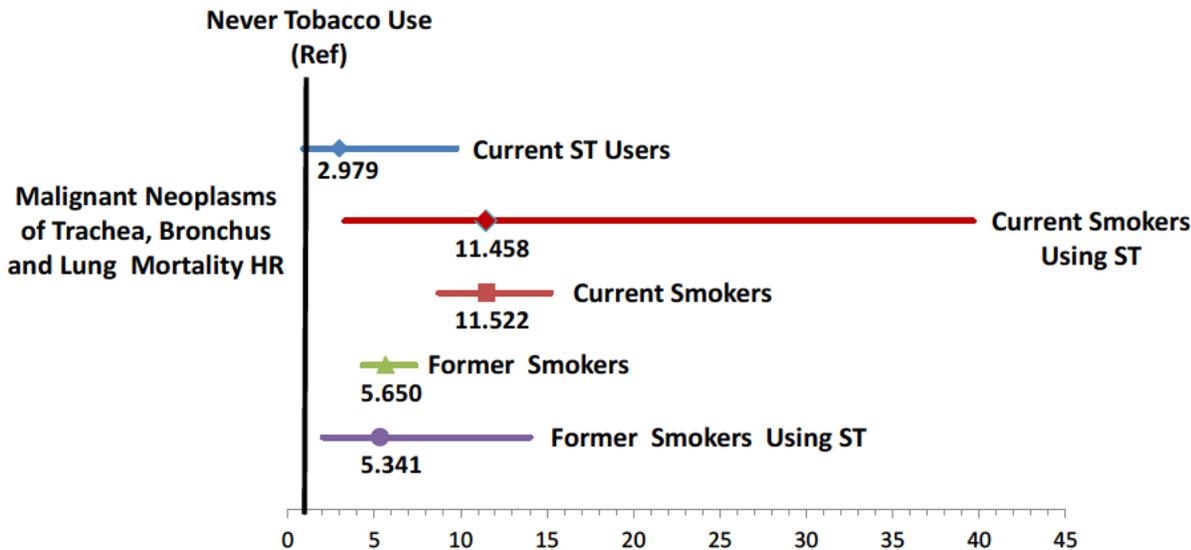
The lung cancer risk of using smokeless tobacco is much lower than smoking cigarettes. Both NHIS and NLMS datasets contained very few reports of deaths associated with lung cancer in exclusive ST users (Section 6.1, Table 6.1-7). These low incidences prevented calculation of a reliable estimate of lung cancer hazard ratios (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 (Section 6.1, Table 6.1-8).

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 2.3-11. 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

¹⁷ 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).

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 2.3-11: Mortality Hazard Ratios^a from Neoplasms of the Trachea, Bronchus, and Lung: Adjusted Hazard Ratio Estimates for Various Tobacco Use Practices Compared to Never-Tobacco Users



^a 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) (Section 7.4.1 Linked Mortality Analysis).

Published epidemiology studies report mixed outcomes of possible association between ST use and lung cancer (Section 6.1; Table 6.1-8). 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. (Andreotti et al., 2016) provided lung cancer estimates using data from the Agricultural Health Study for ST users (Section 6.1; Table 6.1-8). 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 (Section 6.1; Tables 6.1-7, 6.1-8 and 6.1-9), 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 the candidate product 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.

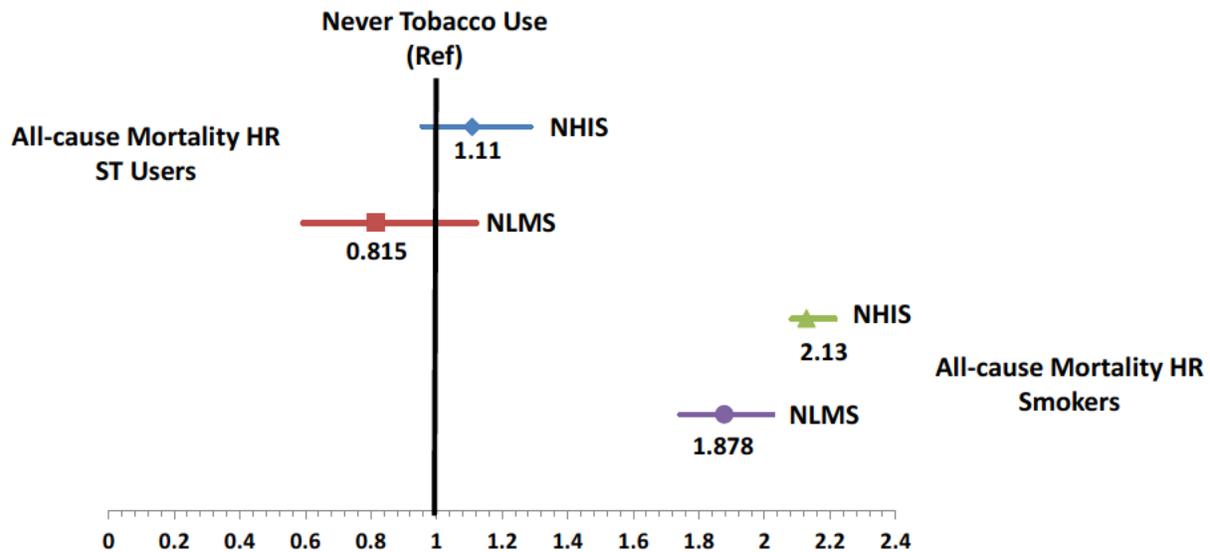
- Second, our analysis of the NLMS dataset indicates that dual users (current cigarette smokers who use ST) have similar lung cancer risk to exclusive cigarette smokers, providing further evidence that using ST does not add to the lung cancer risk of cigarette smoking.
- Third, our analysis of the NLMS dataset indicates that former cigarette smokers who use ST have similar lung cancer risk to former smokers who do not use tobacco products.

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

Figure 2.3-12 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 the candidate product, 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. As discussed in Section 6.1.2.1.3, however, some researchers have noted 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 is not intended to suggest that ST use is without risk.

Figure 2.3-12: All-Cause Mortality Hazard Ratios^a in ST users and Smokers Compared to Never Users



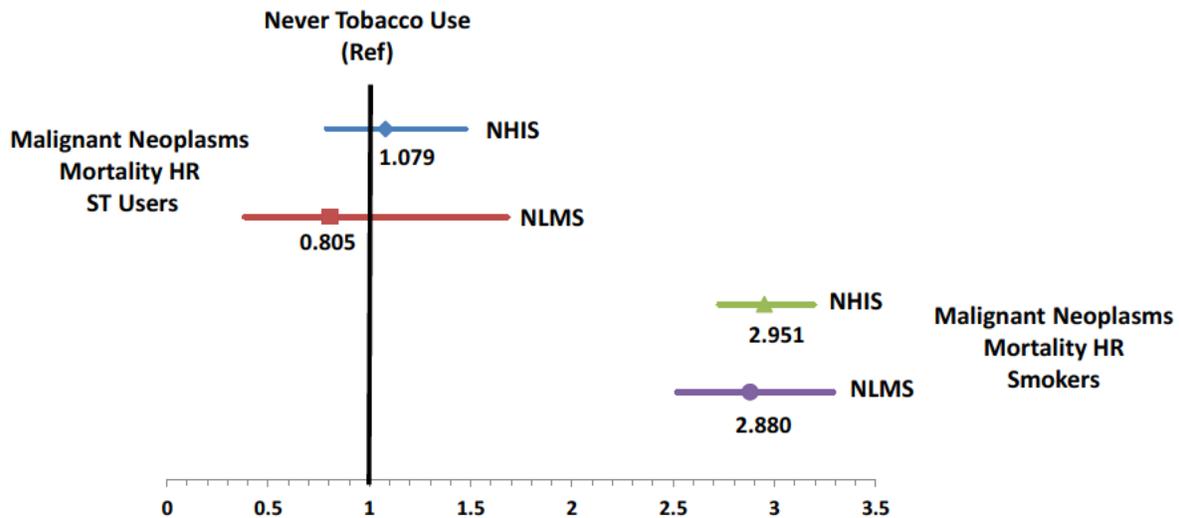
^a Estimates derived from Cox proportional hazards analysis of the NLMS datasets with covariate adjustments (gender, race [white, non-white], age, education, family income, self-reported health status, tobacco use, and cigarettes per day. The analysis

was conducted on all respondents (P4 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters) (Section 7.4.1 Linked Mortality Analysis).

2.3.3.5.3. 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 2.3-13 shows the estimated mortality HR from malignant neoplasms (all types) from the NHIS and NLMS data sets 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 2.3-13: Mortality Hazard Ratios from Malignant Neoplasms in ST users and Smokers Compared to Never Users



^a 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) (Section 7.4.1 Linked Mortality Analysis).

2.3.3.6. Conclusions – Scientific Health Risk Evidence Supporting Market Authorization

Based principally on our analysis of well conducted, public, nationally representative data sets – 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 pulmonary exposure. 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 these constituents and favorable changes in biomarkers of chronic inflammation.
- Switching completely to the candidate product 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 data sets 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, the candidate product presents significantly lower disease risks compared to cigarettes. Our analysis of the NLMS and NHIS data sets 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 (Table 6.1-10).

These conclusions support the scientific validity of the proposed claim that switching completely from cigarettes to the candidate product reduces risk of lung cancer.

2.3.4. Effect of Marketing on Consumer Understanding and Perceptions

We developed the proposed modified risk claim language to be clear, relevant, believable and easily understandable. We tested claim comprehension and risk perceptions (relative and absolute) in adult users and non-users (former and never users) of tobacco products. Based on our study, we demonstrate that:

- The proposed claim language is clear, relevant, believable, and easily understandable; and
- Adult users and non-users understand the proposed advertising and labeling and are not misled to believe the candidate product is without risk.

A large majority of adult smokers have preexisting and deeply rooted misperceptions about the health risks of ST compared to cigarettes. The intended outcome of our proposed claim is to influence adult smokers' product choices by providing accurate information about these risks. Over time, and with repeated exposures, this information may help adult smokers better understand the relative risks of the candidate product and cigarettes and encourage them to switch completely to the candidate product.

ALCS designed a perception and behavior program to develop and test modified risk claims (Section 6.2; Figure 6.2-2) for comprehension and risk perceptions. We conducted the Claim Comprehension and Intentions (CCI) Study (Section 7.3.2) among adult users and non-users 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) and behavioral intentions regarding the candidate product (Section 7.3.2).

The CCI Study was an online study involving 5,871 adult (legal age to use tobacco products [LA] and older) users and non-users 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.¹⁸ We designed this study with adequate sample size to provide 80% statistical power for detecting differences attributable to exposure to the proposed claim in the behavioral intentions of each subgroup. 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 (Table 2.3-3). The pooled LA-24 year old participants from the main sample and oversample were assigned to either user or non-user subgroups.

Table 2.3-3: Claims Comprehension and Intentions Study Sample Size and Study Subgroups

	Current Adult Tobacco Users				Adult Non-users		Total Participants
	ASPQ	ASNPQ	Dual Users	MST Users	Former Users	Never Users	
Test Condition	406	398	422	432	402	402	2,462
Control Condition	401	403	418	439	404	400	2,465
Total	807	801	840	871	806	802	4,927

Source: CCI Study Report (Appendix 7.3.2-1; Table 4)

ASPQ=Adult Smokers Planning to Quit; ASNPQ=Adult Smokers Not Planning to Quit; Dual Users=Cigarette Smokers and MST Users; MST=Moist Smokeless Tobacco

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 the candidate product 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

¹⁸ 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).

federally mandated warnings, which were rotated within the study, but without the proposed claim.

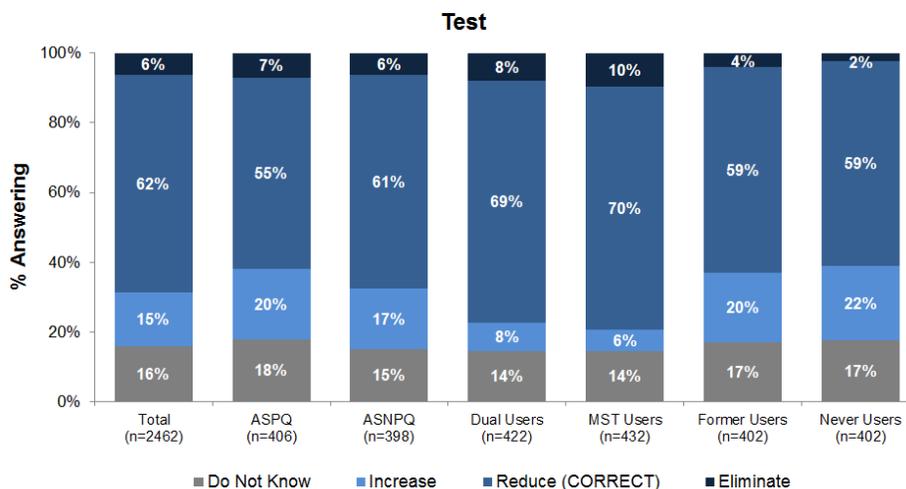
Participants answered questions on risk perceptions before (pre-test) and after (post-test), which helped us understand the influence of participants’ incoming beliefs on Test and Control differences and isolate the impact of the proposed claim.

2.3.4.1. Consumers understand the proposed advertising and labeling and are not misled to believe the candidate product 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 (Section 7.3.2).

Figure 2.3-14: 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: CCI Study Report (Appendix 7.3.2-1, Table 6)

Overall, as shown in Figure 2.3-14, a clear majority of participants 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 the candidate product, selected the correct response. The majority of Low Health Literacy (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 the candidate product as eliminating the risk of lung cancer. To the contrary, only

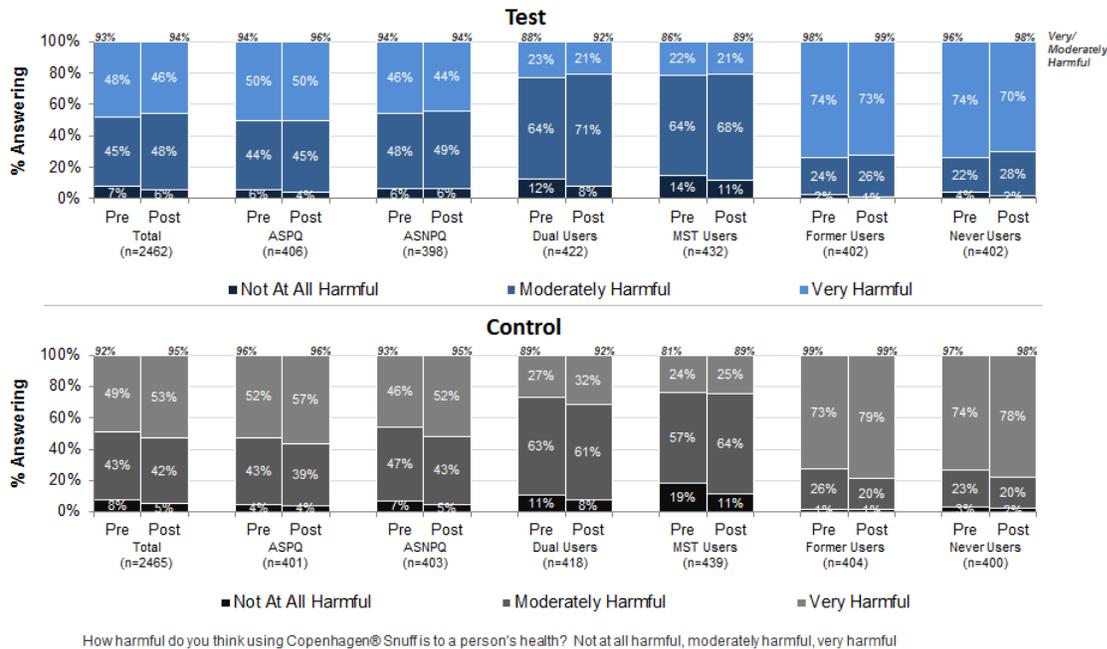
6% of all participants who viewed the claim (181 of 2933) indicated that the candidate product eliminated lung cancer risk. Among current tobacco user subgroups, this perception ranged from 6% (ASNPQ) to 10% (MST users). Tobacco non-user subgroups were less likely to hold this perception, with only 4% of former users and 2% of never users perceiving that the candidate product eliminated lung cancer risk. In a recent study involving modified risk statements associated with a commercial ST product, Fix et al., (2017) reported similar observations; a proportion of the respondents (specific data not included in the manuscript) selected “no risk” after viewing the claim.

We gain additional insights into these respondents by further analysis of ([Appendix 7.3.2-9; Table 6](#)) incoming beliefs among those (n=181) who selected “eliminates” lung cancer risk. In this analysis, 19% (35 of the 181) at pre-test already believed that the candidate product is extremely unlikely to cause lung cancer and exposure to the claim did not change their prior risk perception. Therefore, their response to the targeted question remained consistent with their incoming beliefs. The vast majority (71%) of the remaining respondents (129 of the 181) continued to believe that the candidate product has some likelihood of causing lung cancer both before and after claim exposure. For this proportion of participants, a response of “eliminates” the risk of lung cancer is inconsistent with their stated beliefs about the candidate product both pre- and post-exposure.

To further investigate the impact of the claim, we first assessed if the claim led study participants to believe that the candidate product 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 the candidate product. A vast majority (89%-99%) of participants associated some level of harm (“moderately harmful” or “very harmful”) with using the candidate product after exposure to the proposed modified risk claim. Furthermore, viewing the proposed claim did not increase the perception that the candidate product is “Not at all harmful” in any subgroup. This provides evidence that the claim did not lead people to believe the candidate product presents no harm.

Figure 2.3-15: General Harm Associated with the Candidate Product Pre-Post for Test and Control



Source: [Appendix 7.3.2-1; Table 64](#)

ASPQ = Adult Smokers Planning to Quit; ASNPQ = Adult Smokers Not Planning to Quit; MST = Moist Smokeless Tobacco

On average, participants characterized the believability of the proposed claim as either neutral (“neither disagree nor agree”) or positive (“agree”) ([Appendix 7.3.2-1; Table 58a](#)). A subset of participants did not believe the proposed claim. These results corroborate our findings during the claims development research and suggest that pre-existing beliefs about the relative harm of ST products influenced participant responses following initial 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, the disease referenced in our proposed claim. 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 ([Appendix 7.3.2-1; Table 56](#)).

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

2.3.4.2.1. Perceived Absolute Risk of the Candidate Product

The CCI Study corroborates previous reports that a large majority of adult tobacco consumers perceive ST products, including the candidate product, as harmful (Figure 2.3-15). A vast majority of adult tobacco consumers, in both the control and the test groups prior to viewing to the proposed claim, perceived the candidate product as moderately or very harmful. Single exposure to the proposed claim did not alter that perception. Non-users (Former Users, Never Users and LA-24) overwhelmingly perceived the candidate product as very harmful, before and after viewing the proposed claim. A vast majority of MST users (Dual Users and MST Users) perceived the candidate product as either moderately harmful or very harmful, but were less inclined than other groups to describe the candidate product 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 the candidate product 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 the candidate product 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 the candidate product was highly likely to cause lung cancer ($\geq 70\%$ “likelihood of lung cancer occurring”) (Appendix 7.3.2-1; Table 56) even after viewing the proposed claim.

2.3.4.2.2. Perceived Risk of the Candidate Product Relative to Cigarettes and Other ST Products

In general, across all subgroups, single exposure to the proposed claim did not alter relative risk perceptions (Section 6.2). All subgroups ranked cigarette smoking as only slightly more risky than the candidate product, on average. Between 43% and 64% of subgroup participants assigned the same risk to using the candidate product as to smoking cigarettes.

Participants rated the perceived risk of lung cancer from use of the candidate product as slightly lower than smoking cigarettes, on average. Participants rated the perceived risk of general and specific health outcomes from using the candidate product 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 the candidate product than smoking, while they perceived risk for lung cancer as only slightly lower than smoking.

Relative to ST use, most CCI Study participants perceived the candidate product to be equally risky as other snuff/dip/ST products and did not change their perceptions after exposure to the proposed claim. Non-users 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

non-users accurately rated the risks of using the candidate product to be higher than using NRTs, quitting all tobacco use, or never using tobacco products.

These results demonstrate that the proposed claim does not mislead adult tobacco consumers about the relative risk of the candidate product as compared to cigarettes or other ST products.

2.3.4.3. 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 non-users (including LA-24 year olds) understand and do not misinterpret the advertising and labeling with the proposed claim.
- Adult tobacco users and non-users continue to believe that candidate product 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 the candidate product as compared to cigarettes; risk perceptions proved consistent with literature findings in failing to differentiate the substantial difference in risk between the candidate product and cigarettes.
- The non-MST user subgroups (adult smokers, non-users 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 the candidate product, notwithstanding the fact that participants understood the proposed claim and were not misled by it. These results are unsurprising. Prior published studies ([Table 2.3-1](#)) 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 to continue to monitor the impact of the proposed modified risk claim on the risk perceptions of users and non-users of tobacco products.

2.3.5. Effect on Tobacco Use Behavior among Current Users

Based on our assessment of the likelihood of use of the candidate product 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 the candidate product, although modest, with greatest use potential among the adult male smoker subgroup;

- there is no statistically significant increase or decrease in trial or switching behaviors;
- there is no statistically significant increase or decrease in the likelihood of candidate product 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 the candidate product.

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

2.3.5.1. We expect low likelihood that current tobacco product users will begin to use the candidate product upon market authorization of the proposed modified risk claim.

The CCI Study assessed possible changes in tobacco product use intentions as a result of viewing the proposed claim. We provide a brief overview of the CCI Study in Section 2.3.4 above. Based on the results of this CCI Study (Appendix 7.3.2-1), we observe a small increase in likelihood of using the candidate product among current tobacco users as a result of marketing the candidate product with the proposed claim, and a subgroup of adult male smokers expressed greater interest in using the product (Section 6.5, Table 6.5-1). Overall, we believe that a large percentage of current users is unlikely to switch immediately to the candidate product. 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 the candidate product for any tobacco product user subgroup (Table 2.3-4).

Table 2.3-4: Composite Scores (unadjusted means) of Responses Related to Candidate Product 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
ASNPQ 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 - [Appendix 7.3.2-1](#); [Table 7, Table 16](#)

¹ Values represent the unadjusted average score of responses to statements or questions related to trial or use of the candidate product 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 ASNPQ = 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.)

Consistent with their stated reluctance to *try* the candidate product, most groups also indicated no change in intention to *use* the candidate product 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 (ASNPQ) subgroup. Specifically, ASNPQ in the Test condition, after exposure to the proposed claim, reported a modestly higher intention to use than ASNPQ 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 the candidate product and small effect size.

The results were further corroborated by reviewing the proportion of current users indicating *positive affect to try* and *positive affect to use* the candidate product. In simplest terms, “positive affect” refers to a current tobacco user subpopulation that, based on their responses to study questions, appears relatively more likely to try or use the candidate product, as compared to other current tobacco users that express some interest in it. We determined the proportion of respondents having a positive affect to *try* the candidate product 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 with a positive intent to *use* the candidate product (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 2.3-5) a small increase (<2%) in the proportion indicating a positive affect only in the ASNPQ subgroup for the Test condition for both trial and regular use. We further examined the behavioral intentions in adult male smokers, which served as one of the inputs for our population model (Section 2.3.7 and Section 6.5; Table 6.5.1). Thus, while the claim shows impact on only a small proportion of tobacco users, potential trial and use among adult smokers not planning to quit is a favorable outcome.

Table 2.3-5: Proportion of Current Tobacco Users Indicating Positive Affect

Group	Condition	Positive Affect (%) 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

Source: Appendix 7.3.2-1; Table 59 Positive Affect: Try Copenhagen Snuff®; Appendix 7.3.2-1; Table 60 Positive Affect: Use Copenhagen Snuff®

¹ Positive affect was assessed based on a combination of a positive response to intent to purchase the candidate product after reviewing the advertisement along with a composite score of >3.5 for intention to try and use.

Although the single exposure to modified risk messaging in the CCI Study demonstrated only modest effects on participants’ intentions to use the candidate product, 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 the candidate product. Thus, misperceptions may pose a barrier to immediate switching from cigarette smoking to using the candidate product. Communicating accurate risk information about the candidate product is a necessary first step.

2.3.5.2. We found no statistically significant increase or decrease among ATC with respect to the likelihood of dual use involving the candidate product.

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

Over time, as observed in some Scandinavian countries, the Swedish snus experience being most relevant, consumers transition from dual to exclusive use. In Norway many dual users have shown interest in switching to exclusive snus use (Lund & McNeill, 2013). These patterns among Norwegian males suggest that, over time, the prevalence of dual use has declined and exclusive use has increased, resulting in favorable public health outcomes. In Sweden, similarly, lung cancer rates have declined, which may correspond with smoking declines and uptake of ST (Rodu & Cole, 2009). Indeed, these Scandinavian examples may provide a public health roadmap for addressing the harms caused by smoking in the U.S.

Our CCI Study indicated no statistically significant differences ([Appendix 7.3.2-1; Table 28](#)) in intentions to dual use between the Test and Control conditions for any applicable subgroups, after adjusting for covariates.¹⁹

2.3.5.3. There is little likelihood that ATC who adopt the candidate product 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 the candidate product once marketed with the proposed claim, would switch to cigarettes or another higher risk tobacco product. Direct evidence of this theoretical reversion will not be available until FDA authorizes the candidate product to be marketed with the proposed claim.

¹⁹ This was only asked of current cigarette smokers, regardless of current MST use. Also, they were asked specifically about intention to dual use cigs + the candidate product.

In general, tobacco users in our CCI Study expressed little interest in adopting the candidate product, even after viewing the proposed claim. If tobacco users do not adopt the candidate product, the question of switching back to cigarettes is irrelevant. Our conclusions are based on the summary of findings provided in Section 6.3.

Current available evidence, as summarized from the literature in Section 6.3, 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 the candidate product when marketed with the proposed claim would switch back to exclusive cigarette smoking, particularly as they internalize accurate beliefs about the risk differential between the candidate product and cigarettes. If anything, it is reasonable to surmise that the proposed claim will discourage users of the candidate product from switching or reverting back to cigarettes. We will monitor such behaviors during postmarket surveillance.

2.3.5.4. We observed no statistically significant increase or decrease in the likelihood that users who may have otherwise quit using tobacco products will instead use the candidate product.

Current scientific evidence does not lead us to conclude that marketing the candidate product with the proposed claim would hinder a smoker's attempt to quit smoking. Our CCI Study (Appendix 7.3.2-1) 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 ($M = 0.09$), (Appendix 7.3.2-1; Table 66). Using a more robust logistic regression model incorporating key behavioral factors (e.g. product use behavior), these differences were no longer statistically significant (Appendix 7.3.2-1; Table 37). 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.

2.3.5.5. Actual use behavior for the candidate product is well established, stable, and not likely to change.

The candidate product has been on the market for many decades and the actual use behavior is stable and well established, as described in Section 3.2. We expect that, over time, the proportion using the candidate product may increase in response to the proposed modified risk claim, but we do not anticipate changes in actual use behavior (topography of use). We present multiple lines of supporting evidence (Section 3.2; Table 3.2-1) 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. It is difficult, however, to

assess potential effects on real-world topography of use in a premarket setting, so we will monitor any potential impacts during postmarket surveillance.

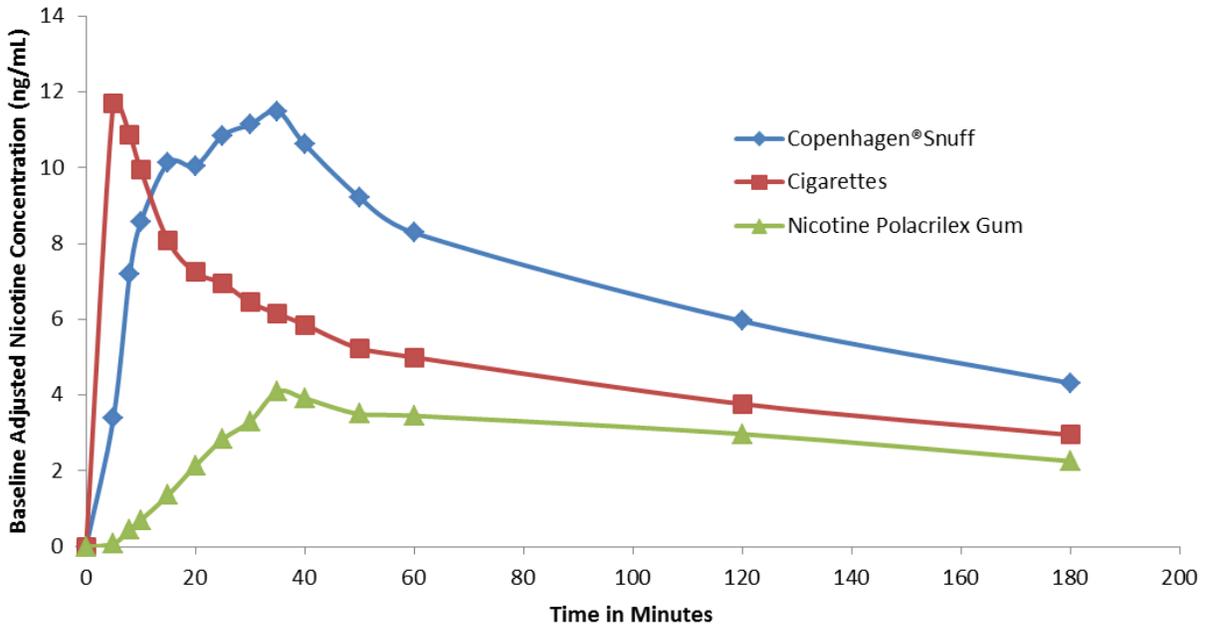
2.3.5.6. The candidate product exhibits greater than, or similar, abuse potential to NRT gum, but lower abuse potential than cigarettes.

We investigated the abuse liability of the candidate product through review of published literature and clinical research. We conducted a randomized, controlled, three-way, crossover clinical study characterizing nicotine pharmacokinetics and subjective effects for the candidate product (manufactured as the grandfathered product), own brand cigarettes and nicotine polacrilex gum (Appendix 7.3.1-1). Figure 2.3-16 summarizes the results of this study. Based on the pharmacokinetic profile of the candidate product and subjective effects (Figure 2.3-16) measured in our study (Section 6.3 and Appendix 7.3.1-1), we conclude that the abuse potential of the candidate product 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.”²⁰ The candidate product satisfies this criterion, because our data indicate that it is less reinforcing than cigarettes and at least as reinforcing as NRT products.

²⁰ Institute of Medicine, 2012. Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, DC: The National Academies Press.

Figure 2.3-16: Nicotine Pharmacokinetic Profile for Copenhagen® Snuff Relative to Own Brand Cigarettes and Nicotine Polacrilex Gum



Source: [Appendix 7.3.1-1; Table 9](#)

2.3.5.7. 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 understanding of the accurate modified risk claim, adjustment of prior beliefs, and encouragement for adult cigarette smokers to switch to the candidate product instead of cigarettes.

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. Indeed such a public health approach, as observed in some Scandinavian countries, may lead to product switching behaviors that reduce the risk of lung cancer and other serious diseases.

Consistent with Institute of Medicine recommendations, the abuse potential of the candidate product is lower than cigarettes and greater than, or similar to, that of NRT products.

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

2.3.6. Effect on Tobacco Use Behavior among Non-users

Youth should not use any tobacco product. In addition to providing the proposed advertising and labeling, Section 4.1 describes our plans to minimize the reach of these communications to unintended audiences, including youth.

Based on 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 demonstrate that market authorization of the proposed claim should result in minimal change in likelihood of use of the candidate product among non-users.

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

It is difficult to predict the impact of our proposed claim on various non-user groups. We propose a comprehensive postmarket surveillance program (Section 8.1) to monitor for unanticipated and undesirable events related to the use of the candidate product in non-users, particularly youth.

2.3.6.1. We expect no increase or decrease in the likelihood of initiation of candidate product use in adult non-users (never and former users), LA-24 non-users and youth.

In the CCI Study (Section 2.3.4 and Appendix 7.3.2-1), we observed no significant ($p>0.05$) increase or decrease in the intent to try or use the candidate product among adult non-users, 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 positive affect to try and use by combining behavioral intentions with intention to purchase (Section 6.3). Before exposure to the proposed claim, non-users in both the test and control conditions expressed very low intention to try or use the candidate product. After exposure to the proposed claim, non-users remained disinterested, as measured by unchanged intentions to try or use the candidate product (Table 2.3-6). Less than 3 percent of participants in any non-user study group indicated a positive affect to try the candidate product (Table 2.3-7). We observed no significant ($p>0.05$) changes in likelihood of initiation among LA-24 non-users.

Overall, there is no reason to expect an increase in initiation of the candidate product when marketed with the proposed modified risk claim, based on the lack of interest in the candidate product by the population of non-users (adults and young adults LA-24) after exposure to that claim. We do not anticipate youth initiation rates for the candidate product to exceed rates currently observed for the ST category.

Table 2.3-6: Average Composite Scores for Intention to Try and Use the Candidate Product among Adult Non-users

	Never Users		Former Users		Non-users LA-24	
	Test	Control	Test	Control	Test	Control
Base Size	402	400	402	404	401	403

		Never Users		Former Users		Non-users LA-24	
		Test	Control	Test	Control	Test	Control
Intention to Try ¹	Pre-exposure	1.3	1.4	1.4	1.3	1.5	1.4
	Post-exposure	1.2	1.3	1.3	1.3	1.4	1.4
Intention to Use ²	Pre-exposure	1.3	1.3	1.3	1.3	1.4	1.3
	Post-exposure	1.2	1.3	1.3	1.2	1.4	1.3

Source: [Appendix 7.3.2-1; Table 7](#) (Intention to Try Copenhagen[®] Snuff); [Appendix 7.3.2-1; Table 16](#) (Intention to Use Copenhagen[®] Snuff); [Appendix 7.3.2-1; Table 59](#) Positive Affect: Try Copenhagen[®] Snuff; [Appendix 7.3.2-1; Table 60](#) Positive Affect: 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 the candidate product. 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 2.3-7: Proportion of Adult Non-users Indicating Positive Affect

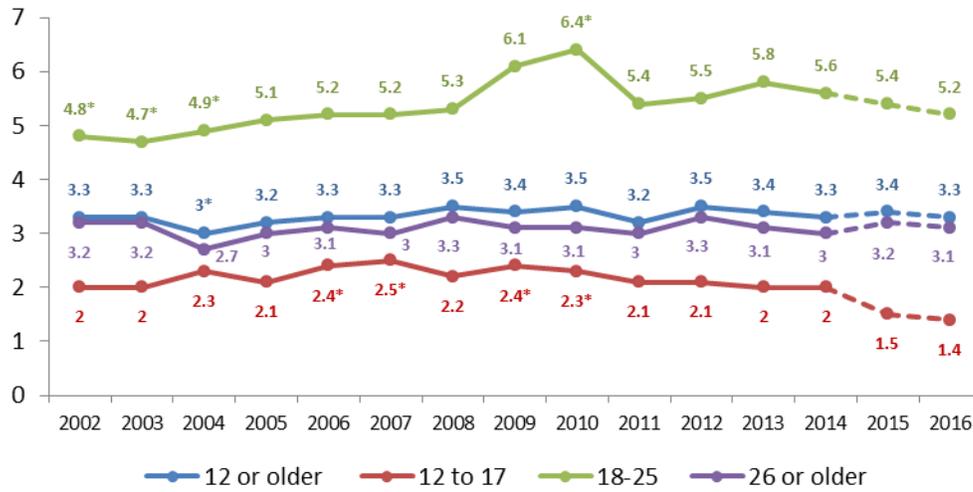
Positive Affect ¹		Never Users		Former Users		Non-users LA-24	
		Test	Control	Test	Control	Test	Control
Base Size		402	400	402	404	401	403
Positive Affect (Try)	Pre-exposure	2.49%	2.25%	2.99%	1.73%	1.75%	2.48%
	Post-exposure	1.74%	2.00%	2.49%	1.73%	2.24%	1.74%
Positive Affect (Use)	Pre-exposure	2.49%	2.25%	2.49%	1.98%	2.74%	2.73%
	Post-exposure	1.74%	2.00%	2.74%	1.73%	2.00%	1.74%

¹ Positive affect was assessed based on a combination of a positive response to intent to purchase the candidate product after reviewing the advertisement along with a composite score of >3.5 for intention to try and use. [Appendix 7.3.2-1; Table 59](#) Positive Affect: Try Copenhagen[®] Snuff; [Appendix 7.3.2-1; Table 60](#) Positive Affect: Use Copenhagen[®] Snuff

Data for smokeless tobacco use and risk perception provide additional insight in support of this conclusion.

Over the past decade, the overall prevalence of ST use in youth, young adults, and older consumers has been low and relatively stable in the U.S. over the past decade (Figure 2.3-17). A comprehensive review of the literature (Section 7.5.3-1 and 7.5.3-2) indicates a much lower prevalence of ST use among youth and young adults compared to smoking.

Figure 2.3-17: Past Month Smokeless Tobacco Use Among People Aged 12 Years or Older, by Age Group: Percentages, 2002-2016



Sources: 2002-2014: Reproduced 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.

*Denotes a statistically significant difference between this estimate and the 2014 estimate at the 0.05 level. Significance is indicated only for years 2002 to 2014.

Note: The data for the years 2015 and 2016 (represented above by the dashed lines) should be compared with caution to prior years' data. Before 2015, smokeless tobacco included chewing tobacco or snuff/dip. In 2015 and 2016, smokeless tobacco includes snuff, dip, chewing tobacco and snus.

Also over the past decade, an increasing proportion of youth perceive ST products as less hazardous than cigarettes. Data from the Monitoring the Future (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 (Section 6.4; Table 6.4-8). 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 stable 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 the candidate product beyond currently-observed rates. If anything, these patterns suggest that the proposed modified risk claim is unlikely to substantially influence ST use among youth.

A variety of factors influence youth ST trial and use. Among children and adolescents, familial use of ST is strongly related to trial and initiation, while in young adults, peer use has a greater influence. Trial and regular ST 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, marketing the candidate product with the proposed claim is unlikely to impact initiation in youth and young adults beyond currently-observed rates for the ST category. We plan to monitor this effect in our proposed postmarket surveillance program.

In summary, results from our CCI Study among non-users and observations from national surveys among youth do not lead us to conclude that marketing the candidate product with the proposed claim will increase initiation among non-user groups.

2.3.6.2. We expect no increase or decrease in the likelihood that non-users who may adopt the candidate product 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 non-users who may adopt the candidate product, 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 the candidate product is marketed with the proposed claim, following FDA authorization. We will monitor this behavior (sometimes referred to as the *gateway effect*) during postmarket surveillance.

Non-users in our CCI Study expressed no interest in adopting the candidate product, even after reviewing the modified risk claim. This suggests that the likelihood of 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 non-users (adult and youth) will switch to cigarettes after adopting ST, after adjusting for the factors that typically influence tobacco product use behavior (Section 6.4 and Section 7.5.3-1 and 7.5.3-2).

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 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 (Section 6.4, Figure 6.4-4).

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 that takes into account the many factors (e.g., peer pressure, marketing and advertising, future regulatory policies) that influence product use behavior in the real-world.

2.3.6.3. There is no evidence that former users of tobacco products will reinitiate use with the candidate product.

We present evidence that former users are not likely to reinitiate use with the candidate product. We observed no significant ($p>0.05$) increase in intentions to try and use the candidate product among former tobacco product users after reviewing the proposed claim in our CCI Study (Table 2.3-7). The published literature on this behavior pattern for ST use in general, is sparse (Section 7.5.3-1 and 7.5.3-2).

2.3.6.4. Conclusions – Effect on Tobacco Use Behavior among Non-users

We conclude the following, based on the results of our CCI study in non-users of tobacco products (and also non-users 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) non-users, will adopt the candidate product in the presence of advertising and labeling materials with the proposed claim.
- There is low likelihood that marketing the candidate product 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 non-users would adopt the candidate product 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 non-users from marketing the candidate product with the proposed claim. Direct evidence of underage use and non-users adopting the candidate product can only be obtained under real-world conditions during postmarket surveillance (Section 8.1).

2.3.7. Effect 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.” FDCA §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 (ALCS Cohort Model) to estimate the overall impact of market authorization of the proposed modified risk claim on the population as a whole, including users and non-users of tobacco products.

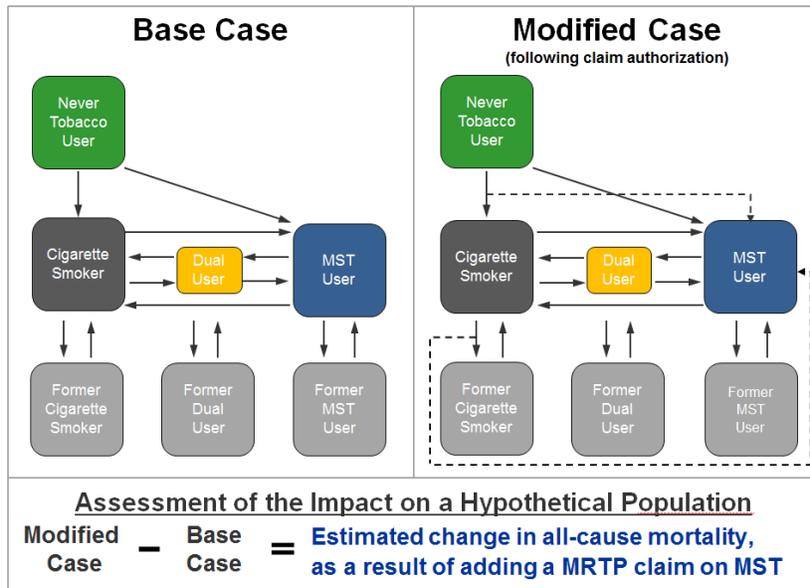
We applied the ALCS Cohort Model to estimate the net benefit to the population, using both single-cohort and multi-cohort approaches. The results demonstrate a modest reduction in overall mortality in the U.S. population if FDA authorizes the candidate product to be marketed with the proposed claim. We conclude that net benefit outweighs the risks of market authorization of the proposed claim.

Predictive computational modeling is a highly technical field with a lexicon derived from mathematics, statistics, epidemiology, and other disciplines. Below, we provide a more technical summary of the ALCS Cohort Model, focusing on its framework and applications, results, and assumptions and limitations.

2.3.7.1. Framework and Applications of the ALCS Cohort Model

The ALCS Cohort Model (Boone et al., 2016) (Section 7.4.2) estimates the overall impact of market authorization of the proposed modified risk claim on the population as a whole, including users and non-users of tobacco products. To develop and validate this 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). We describe the development and validation of the ALCS Cohort Model in Section 7.4.2. The model consists of 29 states and 30 transitions (Figure 2.3-18).

Figure 2.3-18: Modeling Effect of Adding an MRTP Claim on an Existing Product



The ALCS Cohort Model estimates the overall impact of market authorization of the proposed modified risk claim for Copenhagen® Snuff Fine Cut (the candidate product) on the U.S. population by comparing the survival of hypothetical populations in two scenarios:

1. 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 moist smokeless tobacco (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)].
2. Modified Case Scenario – This scenario reflects a future state in which authorization of the proposed claim yields a change in the transitions within this population.

In order to conduct these estimates:

1. We estimate the impact at the MST category level by determining the number of lives saved in a single cohort of one million males starting at age 13 years.
2. We estimate the number of lives saved in a representative, U.S. native-born male population by extending the single-cohort model to a time-staggered, multi-cohort model. The transitions within the male U.S. population are determined from category level information.
3. We obtain the number of lives saved after authorization of the proposed claim by applying the current market share of the candidate product to adjust the category level estimates from the multi-cohort model to scale. The impact on the population for the candidate product can only be derived from the category level estimates.

The ALCS model is unique in several aspects:

1. The Base Case Scenario takes into consideration the tobacco use behaviors in the population for *both* cigarettes and MST. We focus on cigarettes and MST, which are the predominant forms of tobacco use, are relevant to this application, and have long histories of use that provide reliable transition probabilities.
2. We use a time-staggered, multi-cohort approach that, relative to the single cohort approach, provides more realistic estimates of the native-born male U.S. population.
3. We estimate the net benefit of FDA authorization of the proposed claim specifically for the candidate product based on current market share. Market share data for Copenhagen® Snuff is both realistic and reliable, as the candidate product has been marketed for decades.

Details for the single-cohort analysis are provided in Section 7.4.2.1.2; details for the multiple cohort analysis are presented in Section 7.4.2.1.10. We also provide justification for our population of interest in Section 7.4.2.2.3.

Initially, we modeled a single cohort of one million males, at five-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 (model details are presented in Section 7.4.2). We applied transition probabilities (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 then extended the single-cohort approach to a 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. Finally, we adjusted the results of the multi-cohort approach using the current market share of the candidate product to more realistically estimate the net benefit to the U.S. native-born male population upon authorization of the claim specific to the candidate product.

The **Base Case** is composed of different tobacco use states (non-users 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).

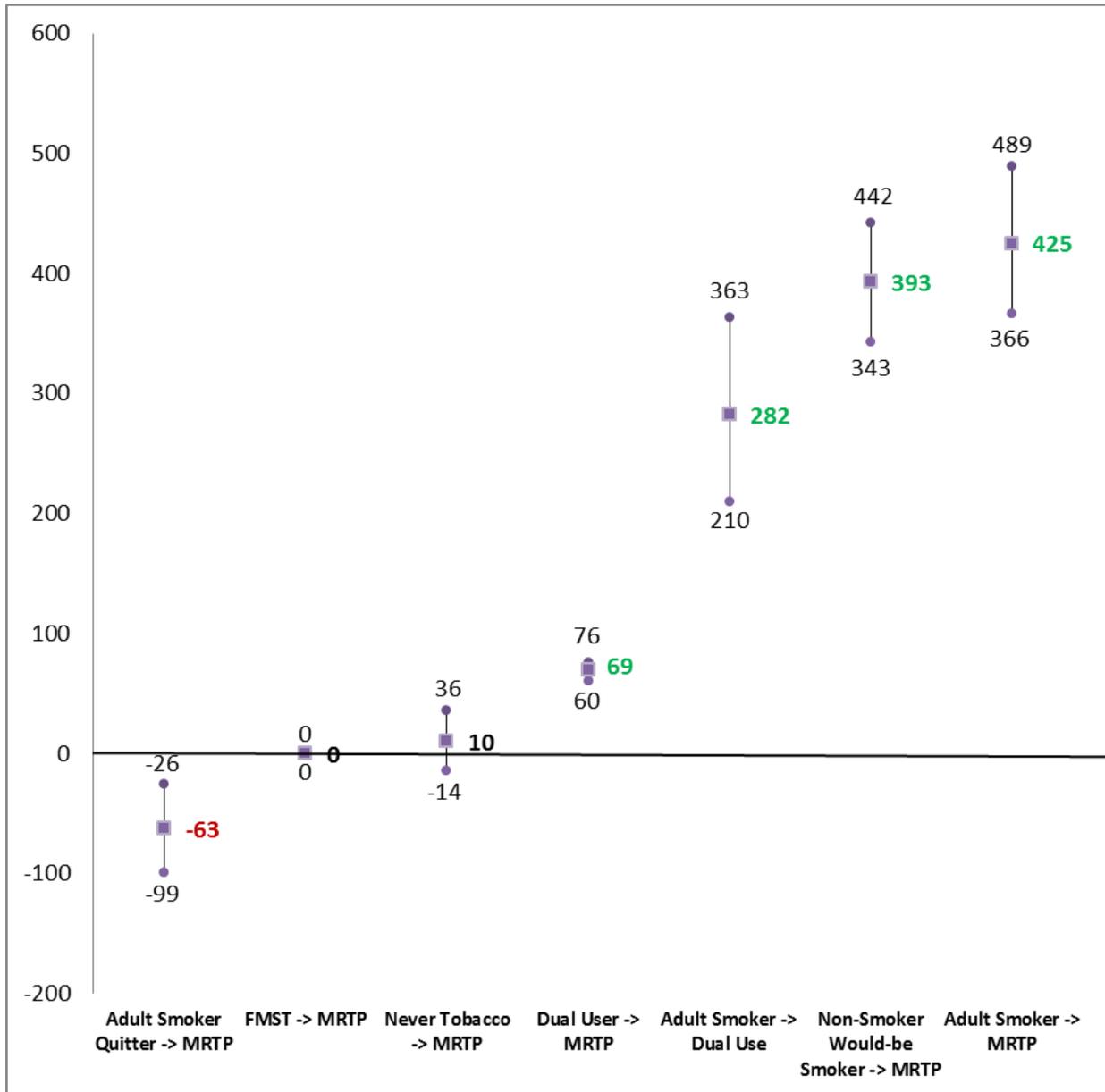
In the **Modified Case**, FDA has authorized the proposed claim. We used an excess relative risk (ERR) of 0.09 for current ST users relative to current smokers, based on the all-cause mortality hazard ratio estimates from the Linked Mortality Analyses (Section 7.4.1). We estimated transition probabilities based on the percent difference between the relevant response of the Test (with claim) and Control (without claim) conditions from the CCI Study (Section 7.3.2) for each scenario and applied them to the Base Case transition rates. While the overall behavioral intentions did not change significantly, our subgroup analysis based on the proportion of males exhibiting positive affect, results in a modest change.

The **Master Case**, the final Modified Case scenario, represents the most likely outcome if FDA authorizes the proposed claim. We present results comparing the number of survivors in the Base Case vs. the Master Case scenarios, to demonstrate that there would most likely be a net benefit to the population.

We then conducted two sets of analyses comparing a series of Modified Cases to the Base Case. In the *first* set, we modified only one transition rate at a time in the Modified Case, while keeping all other transition rates constant to understand the contribution of each individual transition to the observed total net benefit. We conducted a sensitivity analysis by varying only one transition rate at a time over a wide enough range to establish face validity of the transition rate estimates for each Modified Case.

In the *second* set, we constructed the Master Case representing the most likely outcome with all seven transitions being impacted simultaneously [Figure 2.3-19](#). We conducted a sensitivity analysis by varying only one transition rate at a time. The sensitivity analysis also assessed the impact of the ERR by modifying the ERR estimates (0.04-0.5), while keeping all the transition rates fixed. As shown in [Figure 19](#), the highest positive impact (425 additional survivors) results from cigarette smokers' switching to exclusive MST use. Thus, the net benefit of these various transitions results in 1,120 additional survivors.

Figure 2.3-19: Mean Difference in Number of Survivors Between the Master and Base Case Scenarios: Point Estimates and Credible Intervals



Dual User = current cigarette smoker and current MRTP tobacco user; FMST = former moist smokeless tobacco user; MRTP = modified risk tobacco product user.

2.3.7.2. Results of the ALCS Cohort Model

At the category level, the ALCS Cohort Model results demonstrate a modest reduction in overall mortality for the U.S. population, after a follow up period of 60 years, through both the single-cohort and time staggered, multi-cohort approaches.

The single-cohort modeling approach predicts:

- 1,120 additional survivors from a cohort of one million males; and
- 32,856 years of additional life sustained.

The time staggered, multi-cohort approach predicts 93,000 additional survivors, among the U.S. native-born male population.

To better approximate the net population benefit gained by marketing the candidate product with the proposed claim, we adjusted the results to scale using the candidate product's current market share. In this, our most realistic modeling scenario, we find 7,500 additional survivors among the U.S. native-born male population.

These results indicate that authorizing the candidate product to be marketed with the proposed claim results in a modest health benefit to the population as a whole.

2.3.7.3. ALCS Cohort Model Assumptions and Limitations

As with any computational model, the ALCS Cohort Model is based on certain assumptions and limitations, as detailed in Section 6.5. 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 annually based on findings from our postmarket surveillance.

2.3.7.4. Conclusions – Effect on the Population as a Whole

We developed the ALCS Cohort 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.

2.3.8. Overall Conclusion

The scientific evidence presented in this MRTPA satisfies the statutory requirements for a risk modification order and demonstrates that FDA must authorize the proposed modified risk claim. We have shown that:

- the candidate product 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 the candidate product for many decades, and decades of epidemiological evidence from U.S. populations establish its harm reduction potential. This epidemiology evidence is extensive, compelling, and undeniable: Switching completely to the candidate product 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 the candidate product compared to cigarettes. Many adult tobacco users believe that the candidate product 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, particularly dual users, to switch exclusively to the candidate product. In our study, a single exposure to an advertisement containing accurate information about the relative health risks of the candidate product 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 the candidate product 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. The First Amendment guarantees both the right of adult smokers to receive that information from manufacturers and the right of manufacturers to provide it. Over time, and with repeated exposure, this information will help them better understand the relative risks of the candidate product 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 the candidate product, to the benefit of individual smokers and the public health.

We have addressed the five 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.

2.3.8.1. Health Risks of the Tobacco Product

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

2.3.8.2. Effect of Marketing on Consumer Understanding and Perceptions

- Adult tobacco users and non-users (including LA-24 year olds) understand and do not misinterpret the advertising and labeling with the proposed modified risk claim.
- Adult tobacco users and non-users continue to believe that candidate product 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.

2.3.8.3. 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 male smokers, particularly dual users, 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 adult tobacco consumers to use the candidate product instead of cigarettes.
- Our postmarket surveillance will monitor for potential impacts on tobacco use behavior among current users under real-world conditions
- The candidate product has lower abuse potential than cigarettes and greater than, or similar to, that of NRT products based on the pharmacokinetic profile of the candidate product and subjective effects measured in our study as well as the published literature.

2.3.8.4. Effect on Tobacco Use Behavior among Non-users

- Former and never users of tobacco products, including young adult (LA-24 year old) non-users, have minimal intent to use the candidate product, which does not change after reviewing the proposed claim.
- There is low likelihood that the candidate product 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 non-users would adopt the candidate product 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 non-users adopting the candidate product 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).

2.3.8.5. Effect on the Population as a Whole

The ALCS Cohort 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.

2.3.9. Literature Cited

- Ajzen, I. (1985). From Intentions to Actions: A Theory of Planned Behavior *Action Control*: Springer, Berlin, Heidelberg.
- Anderson, C. M., Burns, D. M., Dodd, K. W., & Feuer, E. J. (2012). Chapter 2: Birth-cohort-specific estimates of smoking behaviors for the U.S. population. *Risk Analysis*, 32 Suppl 1, S14-24. doi:10.1111/j.1539-6924.2011.01703.x
- Andreotti, G., Freedman, N. D., Silverman, D. T., Lerro, C. C., Koutros, S., Hartge, P., . . . Sandler, D. P. (2016). Tobacco use and cancer risk in the Agricultural Health Study. *Cancer Epidemiology, Biomarkers & Prevention*, 29(29), 1538-7755. doi:10.1158/1055-9965.epi-16-0748
- Biener, L., Nyman, A. L., Stepanov, I., & Hatsukami, D. (2014). Public education about the relative harm of tobacco products: an intervention for tobacco control professionals. *Tob Control*, 23(5), 385-388. doi:10.1136/tobaccocontrol-2012-050814
- Boone, R. J., Muhammad-Kah, R. S., Pithawalla, Y. B., Wei, L., Frost-Pineda, K., & Gogova, M. (2016). *Combining Statistical and Compartmental Models for Use in Tobacco Product Risk Assessments*. Paper presented at the Conference on Statistical Practice, San Diego.
- Borgerding, M. F., Bodnar, J. A., Curtin, G. M., & Swauger, J. E. (2012). The chemical composition of smokeless tobacco: a survey of products sold in the United States in 2006 and 2007. *Regulatory Toxicology and Pharmacology*, 64(3), 367-387.
- Borland, R., Cooper, J., McNeill, A., O'Connor, R., & Cummings, K. M. (2011). Trends in beliefs about the harmfulness and use of stop-smoking medications and smokeless tobacco products among cigarettes smokers: Findings from the ITC four-country survey. *Harm Reduct J*, 8, 21-7517.
- Borland, R., Li, L., Cummings, K. M., O'Connor, R., Mortimer, K., Wikmans, T., . . . McNeill, A. (2012). Effects of a Fact Sheet on beliefs about the harmfulness of alternative nicotine delivery systems compared with cigarettes. *Harm Reduct J*, 9, 19-7517.
- Brunnemann, K. D., Qi, J., & Hoffmann, D. (2002). Chemical profile of two types of oral snuff tobacco. *Food and chemical toxicology*, 40(11), 1699-1703.
- Brunnemann, K. D., Scott, J. C., & Hoffmann, D. (1982). N-Nitrosomorpholine and other volatile N-nitrosamines in snuff tobacco. *Carcinogenesis*, 3(6), 693-696.
- Callery, W. E., Hammond, D., O'Connor, R. J., & Fong, G. T. (2011). The appeal of smokeless tobacco products among young Canadian smokers: the impact of pictorial health warnings and relative risk messages. *Nicotine Tob Res*, 13(5), 373-383. doi:10.1093/ntr/ntr013
- Capella, M. L., Taylor, C. R., & Kees, J. (2012). Tobacco Harm Reduction Advertising in the Presence of a Government-Mandated Warning. *Journal of Consumer Affairs*, 46(2), 235-259. doi:10.1111/j.1745-6606.2012.01229.x
- Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health(HHS Publication No. SMA 15-4927, NSDUH Series H-50). Retrieved from <http://www.samhsa.gov/data/>

- Center for Behavioral Health Statistics and Quality. (2017). *Results from the 2016 national survey on drug use and health: detailed tables*. Retrieved from <https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf>
- Chang, J. T., Levy, D. T., & Meza, R. (2017). Examining the Transitions between Cigarette and Smokeless Tobacco Product Use in the United States Using the 2002-2003 and 2010-2011 Longitudinal Cohorts [Epub ahead of print]. *Nicotine & tobacco research*. doi:10.1093/ntr/ntx251
- Choi, K., Fabian, L., Mottey, N., Corbett, A., & Forster, J. (2012). Young adults' favorable perceptions of snus, dissolvable tobacco products, and electronic cigarettes: findings from a focus group study. *American journal of public health, 102*(11), 2088-2093.
- Djordjevic, M. V., Brunneemann, K. D., & Hoffmann, D. (1989). Identification and analysis of a nicotine-derived N-nitrosamino acid and other nitrosamino acids in tobacco. *Carcinogenesis, 10*(9), 1725-1731.
- Fisher, M. T., Bennett, C. B., Hayes, A., Kargalioglu, Y., Knox, B. L., Xu, D., . . . Gaworski, C. L. (2012). Sources of and technical approaches for the abatement of tobacco specific nitrosamine formation in moist smokeless tobacco products. *Food and chemical toxicology, 50*(3-4), 942-948.
- Fix, B. V., Adkison, S. E., O'Connor, R. J., Bansal-Travers, M., Cummings, K. M., Rees, V. W., & Hatsukami, D. K. (2017). Evaluation of modified risk claim advertising formats for Camel Snus. *Health education journal, 76*(8), 971-985. doi:10.1177/0017896917729723
- Godin, G., & Kok, G. (1996). The theory of planned behavior: a review of its applications to health-related behaviors. *Am J Health Promot, 11*(2), 87-98. doi:10.4278/0890-1171-11.2.87
- Haddock, C. K., Lando, H., Klesges, R. C., Peterson, A. L., & Scarinci, I. C. (2004). Modified tobacco use and lifestyle change in risk-reducing beliefs about smoking. *American journal of preventive medicine, 27*(1), 35-41.
- Hatsukami, D., Joseph, A. M., Lesage, M., Jensen, J., Murphy, S. E., Pentel, P. R., . . . Hecht, S. S. (2007). Developing the science base for reducing tobacco harm. *Nicotine & Tobacco Research, 9*(Suppl 4), S537-S553.
- Hoffmann, D., & Adams, J. D. (1981). Carcinogenic tobacco-specific N-nitrosamines in snuff and in the saliva of snuff dippers. *Cancer research, 41*(11 Pt 1), 4305-4308.
- Hoffmann, D., Adams, J. D., Lisk, D., Fisenne, I., & Brunneemann, K. D. (1987). Toxic and carcinogenic agents in dry and moist snuff. *Journal of the National Cancer Institute, 79*(6), 1281-1286.
- Hoffmann, D., Djordjevic, M. V., Fan, J., Zang, E., Glynn, T., & Connolly, G. N. (1995). Five leading U.S. commercial brands of moist snuff in 1994: assessment of carcinogenic N-nitrosamines. *Journal of the National Cancer Institute, 87*(24), 1862-1869.
- Hoffmann, D., Harley, N. H., Fisenne, I., Adams, J. D., & Brunneemann, K. D. (1986). Carcinogenic agents in snuff. *Journal of the National Cancer Institute, 76*(3), 435-437.
- Lee, P. N., & Hamling, J. (2009). Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC medicine, 7*, 36.
- Lund, K. E., & McNeill, A. (2013). Patterns of dual use of snus and cigarettes in a mature snus market. *Nicotine Tob Res, 15*(3), 678-684. doi:10.1093/ntr/nts185
- Miech, R., Schulenberg, J. E., Johnston, L. D., Bachman, J. G., O'Malley, P. M., & Patrick, M. E. (2017). *National adolescent drug trends in 2017: Findings released. (Table 16)*. Retrieved from Monitoring the Future: Ann Arbor, MI.: <http://www.monitoringthefuture.org/Johnston>
- O'Connor, R. J., Hyland, A., Giovino, G. A., Fong, G. T., & Cummings, K. M. (2005). Smoker awareness of and beliefs about supposedly less-harmful tobacco products. *American journal of preventive medicine, 29*(2), 85-90.

- O'Connor, R. J., McNeill, A., Borland, R., Hammond, D., King, B., Boudreau, C., & Cummings, K. M. (2007). Smokers' beliefs about the relative safety of other tobacco products: findings from the ITC collaboration. *Nicotine & Tobacco Research*, 9(10), 1033-1042.
- Peiper, N., Stone, R., van, Z. R., & Rodu, B. (2010). University faculty perceptions of the health risks related to cigarettes and smokeless tobacco. *Drug and alcohol review*, 29(2), 121-130.
- Richter, P., Hodge, K., Stanfill, S., Zhang, L., & Watson, C. (2008). Surveillance of moist snuff: total nicotine, moisture, pH, un-ionized nicotine, and tobacco-specific nitrosamines. *Nicotine & Tobacco Research*, 10(11), 1645-1652.
- Rodu, B., & Cole, P. (2009). Lung cancer mortality: comparing Sweden with other countries in the European Union. *Scandinavian journal of public health*, 37(5), 481-486.
- Sami, M., Timberlake, D. S., Nelson, R., Goettsch, B., Ataian, N., Libao, P., & Vassile, E. (2012). Smokers' perceptions of smokeless tobacco and harm reduction. *Journal of public health policy*, 33(2), 188-201. doi:IO.I057/jphp.2012.9
- Smith, S. Y., Curbow, B., & Stillman, F. A. (2007). Harm perception of nicotine products in college freshmen. *Nicotine & Tobacco Research*, 9(9), 977-982.
- Surgeon General Report, & U.S. Department of Health and Human Services. (2004). The Health Consequences of Smoking: A Report of the Surgeon General. Washington, DC: U.S. Government Printing Office.
- Tam, J., Day, H. R., Rostron, B. L., & Apelberg, B. J. (2015). A systematic review of transitions between cigarette and smokeless tobacco product use in the United States. *BMC public health*, 15, 258. doi:10.1186/s12889-015-1594-8
- Tomar, S. L., & Hatsukami, D. K. (2007). Perceived risk of harm from cigarettes or smokeless tobacco among U.S. high school seniors. *Nicotine & tobacco research*, 9(11), 1191-1196.
- United States Department of Health and Human Services. Substance Abuse and Mental Health Services Administration. Center for Behavioral Health Statistics and Quality. (2016). *National Survey on Drug Use and Health, 2014*. Retrieved from: <http://doi.org/10.3886/ICPSR36361.v1>
- Vineis, P., Alavanja, M., Buffler, P., Fontham, E., Franceschi, S., Gao, Y. T., . . . Doll, R. (2004). Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst*, 96(2), 99-106.
- Wang, Y., Sung, H.-Y., Yao, T., Max, W., & Lightwood, J. (2016). Factors associated with short-term transitions of non-daily smokers: socio-demographic characteristics and other tobacco product use. *Addiction*, 112, 864-872. doi:10.1111/add.13700
- Weaver, S. R., Jazwa, A., Popova, L., Slovic, P., Rothenberg, R. B., & Eriksen, M. P. (2017). Worldviews and trust of sources for health information on electronic nicotine delivery systems: Effects on risk perceptions and use. *SSM - Population Health*, 3, 787-794. doi:<https://doi.org/10.1016/j.ssmph.2017.09.003>
- Winn, D. M., Blot, W. J., Shy, C. M., Pickle, L. W., Toledo, A., & Fraumeni, J. F., Jr. (1981). Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med*, 304(13), 745-749.
- Wray, R. J., Jupka, K., Berman, S., Zellin, S., & Vijaykumar, S. (2012). Young adults' perceptions about established and emerging tobacco products: results from eight focus groups. *Nicotine & tobacco research*, 14(2), 184-190.
- Zeller, M., & Hatsukami, D. (2009). The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US. *Tobacco control*, 18(4), 324-332.