6.4.: EFFECT ON TOBACCO USE INITIATION AMONG NONUSERS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

6.4. EFFECT ON TOBACCO USE INITIATION AMONG NONUSERS

Section 911(g)(4)(C) of the Family Smoking Prevention and Tobacco Control Act states that in order to make the determination that the modified risk tobacco product will benefit the health of individuals and of population as a whole, the Secretary shall take into account:

- ‘‘(C) the increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application.”

In Section VI(A)(3) of the 2012 Draft MRTPA Guidance, FDA further recommends that manufacturers include the following assessments of tobacco use initiation among nonusers:

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

In this section, we use information from comprehensive literature reviews (Section 7.5.3-1 and 7.5.3-2), national surveys, original research and secondary analyses to assess the potential effect of marketing the candidate product with the proposed modified risk claim on tobacco initiation among nonusers, including former users.

Background

We start with an overview of smokeless tobacco (ST) use and initiation in the U.S. (Section 6.4.1). We provide information pertinent to assessing the potential effect of marketing the candidate product with the proposed modified risk claim on initiation separately for adults and youth (Section 6.4.2.1 and Section 6.4.2.2, respectively). Concerning the potential effect on adults, we include information specific to young adults, as well as to the broader adult population. We define *young adults* generally as individuals of legal age to purchase tobacco up to age 24.[1] Unless otherwise noted, when we refer to *adults* in this section, we are referring to all adults (young adults and older adults). In our review relevant to youth, we define *youth* generally as individuals under the legal age permitted to purchase tobacco products, recognizing that data on high school students, 12th graders in particular, may include a proportion of individuals of legal age.

We provide information regarding the likelihood that nonusers who adopt the candidate product will switch to higher risk tobacco products by focusing only on cigarettes, as these present the most significant health risks and generally have the highest use prevalence

[1] The definition of young adult varies slightly across the data sources in this section. For example, our Consumer Comprehension and Intentions Study (Section 7.3.2) includes a sample of adults of legal age to purchase tobacco up to age 24. The Population Assessment of Tobacco and Health Study includes a sample of adults age 18 to 24 years old; whereas, the National Survey on Drug Use and Health includes a sample of adults age 18 to 25 years old.

relative to other tobacco products[2] (Section 6.4.3). We provide study results that assess the potential for former users to reinitiate tobacco use with the candidate product if it was marketed with the proposed modified risk claim (Section 6.4.4) and state our conclusions (Section 6.4.5).

We present findings from research specific to the candidate product with the proposed modified risk claim (Claim Comprehension and Intentions Study for Product Currently Marketed as Copenhagen® Snuff, CCI Study, see Section 7.3.2). We included adult participants who were of legal age to purchase tobacco or older in our CCI Study. We rely on literature and national survey data, including our analyses of these data, when discussing ST initiation and use among youth. In fact, the majority of published research on ST initiation involves the study of youth. Unless otherwise noted, we discuss ST as a general category because it is typically presented in survey and published research as such. We use all of these sources to draw conclusions about the potential effect of marketing the candidate product with the proposed modified risk claim on initiation among nonusers (Table 6.4-1).

Table 6.4-1: Data and Information Sources

Section	National Surveys			Published Literature	CCI Study
	PATH	NSDUH	MTF		
6.4.1 – ST Prevalence and Trends	●	●	●	●	
6.4.2 – Likelihood of Initiation among Nonusers:					
Adults					●
Youth	●	●	●	●	
6.4.3 – Likelihood of Switching to Cigarettes	●			●	●
6.4.4 – Likelihood of Reinitiation among Former Users				[1]	●

PATH = Population Assessment of Tobacco and Health; NSDUH = National Survey on Drug Use and Health; MTF = Monitoring the Future; CCI Study = Claim Comprehension and Intentions Study; ST = smokeless tobacco
[1] Literature is sparse.

It is important to note that definitions of initiation vary in the literature. For example, some studies reviewed for this section define initiation as the first time a user tried a product, while others define initiation as the onset of regular use.

Recognizing how different initiation measures may translate to persistent ST use over time is relevant when evaluating population effects. For example, we present national data that define "recent initiates" as those who report first using ST in the past year. Many of these

[2] With respect to youth, prevalence of past 30-day use of electronic cigarettes surpassed the prevalence of cigarette use among middle school and high school students in 2014 (Arrazola et al., 2015).

individuals, however, will not likely progress to regular use, as evidenced by an examination of tobacco use patterns.

Comparing *ever* use with *current* use can provide useful insights in this regard. For example, in our analysis of 2015 National Survey on Drug Use and Health (NSDUH) data, 5.7% of 12- to 17-year-olds report ever trying ST (i.e., snuff, dip, chewing tobacco or snus); whereas, 1.5% report use of ST in the past 30 days (Table 6.4-2). Only 0.4% report frequent use, defined as use on 20 or more days in the past 30 days. In other words, approximately one quarter of those who ever tried ST report using it in the past 30 days, and fewer than one in ten report frequent use (Table 6.4-2). We observe a similar pattern among 18- to 25-year-olds: 19.7% report ever trying ST; whereas, 5.5% report use in the past 30 days, and 2.7% report frequent use. Likewise, we observe the same behavior patterns in our analyses of Population Assessment of Tobacco and Health (PATH) Wave 1 data (Table 6.4-2).

Table 6.4-2: Prevalence of Ever, Past 30-Day and Frequent Use of Smokeless Tobacco Among Youth and Young Adults

Use Pattern	NSDUH (2015)		PATH, Wave 1 (2013/2014)	
	12-17 year olds	18-25 year olds	12-17 year olds	18-24 year olds
Ever Use	5.7%	19.7%	4.8%	16.9%
Past 30-Day Use	1.5%	5.5%	1.6%	5.3%
Frequent Use[1]	0.4%	2.7%	0.6%	2.4%

Sources: ALCS analyses of NSDUH data (Appendix 6.4-2; Table 1 through Table 6); ALCS analyses of PATH data (Appendix 6.4-1; Table 1 through Table 3; Table 5 through Table 7)
NSDUH = National Survey on Drug Use and Health; PATH = Population Assessment of Tobacco and Heath
[1] Frequent use is defined as use on 20 or more days in the past 30 days.

These data are consistent with patterns of experimentation and suggest that a significant proportion of ever-triers do not progress to or sustain regular use. While trial is a necessary condition for use, it does not sufficiently equate to use. This is an important consideration when assessing the effect of a product on initiation. We report initiation measures drawn from national survey research that are based on first ever use of ST (Section 6.4.1.2). For a significant portion of individuals, these data may reflect experimentation rather than the initiation of regular use. Informed by these observations, we included both intention to try and intention to use measures in our CCI Study.

Conclusions

Based on the results of our study, a comprehensive review of the literature, and analyses of national survey data, we conclude:

- Evidence from the CCI Study indicates no increase or decrease in the likelihood that adult nonusers will initiate use of the candidate product. Adult nonusers express low intentions to try and use the candidate product, and we observed no differences on these measures between those who were exposed to an advertisement with the proposed modified risk claim and those who were exposed to the same advertisement without the claim.
- We expect no increase or decrease in the likelihood that youth will initiate use of the candidate product, based on our assessment of lines of indirect evidence. A variety of factors influences youth use of ST (e.g., peer influences), and the proposed modified risk claim is unlikely to change these factors.
- We expect no increase or decrease in the likelihood that nonusers who may adopt the candidate product will switch to other tobacco products that present higher levels of individual health risk (i.e., cigarettes). ST has been shown not to predict cigarette smoking after adjusting for factors that typically influence smoking. Adult nonusers express little interest in adopting the candidate product; thus, this transition is not a relevant consideration for most nonusers.
- Evidence from the CCI Study indicates no increase or decrease in the likelihood that former users of tobacco will reinitiate use with the candidate product. Adult former tobacco users express low intentions to try and use the candidate product, and we observed no differences on these measures between those who were exposed to an advertisement with the proposed modified risk claim and those who were exposed to the same advertisement without the claim.

Overall, we anticipate minimal unintended consequences among nonusers due to marketing the candidate product with the proposed modified risk claim. We intend to monitor use behavior in nonusers through postmarket surveillance activities (Section 8.1).

6.4.1. Current Snapshot of Smokeless Tobacco Prevalence and Trends

Evaluation of marketing the candidate product with the proposed modified risk claim should be understood in the context of historical initiation and use rates within its product category, as well as in context with other tobacco categories. We present data from national surveys to provide this view.

6.4.1.1. Smokeless Tobacco Use Trends

The overall prevalence of ST use in the U.S. has been relatively stable for over a decade (Figure 6.4-1). Among individuals 12 years of age or older, 3.3 percent reported current use[3] of ST in 2016. Due to changes in how the NSDUH defined ST[4] starting in 2015, data for this year and beyond cannot be compared to prior years. The prevalence estimates for 2015 and

[3] Current use is defined as any use of the tobacco product in the past 30 days.
[4] Starting in 2015, the National Survey on Drug Use and Health expanded the definition of smokeless tobacco to include snus. Thus, ST was defined to include snuff, dip, chewing tobacco and snus.

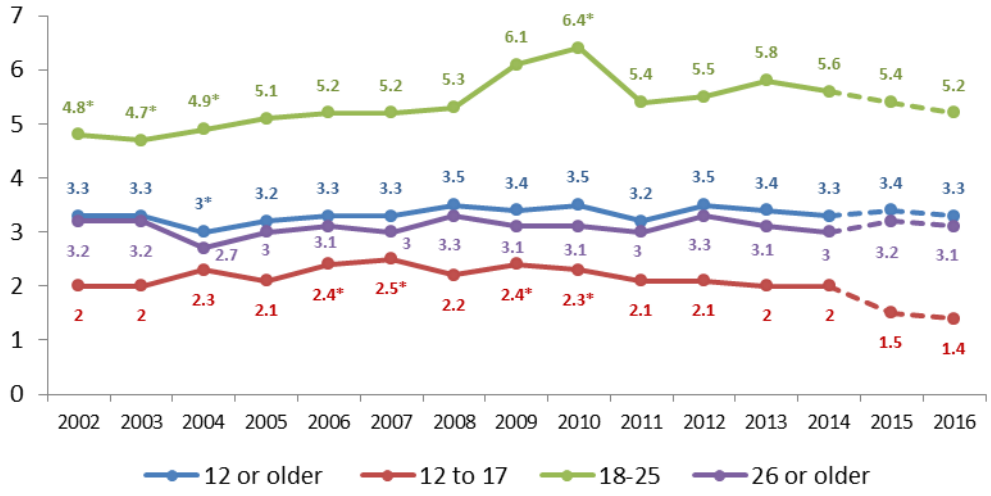
2016, however, suggest the trend remains stable, despite the broader definition of ST used in the recent years.

The prevalence of ST use among 12- to 17-year-olds was 1.4 percent in 2016. The prevalence in 2014, 2 percent, was lower compared to most years from 2006 to 2010 and not statistically different from the prevalence in other years since 2002. The estimates since 2014 suggest that prevalence of ST use among 12- to 17-year-olds remains low.

Prevalence among 18- to 25-year-olds was 5.2 percent in 2016. The prevalence in 2014, 5.6 percent, was lower compared to a recent peak in 2010 and not statistically different from other years since 2005. The estimates since 2014 suggest that prevalence of ST use among 18 to 25-year-olds remains below the recent peak.

Among those 26 years and older, the prevalence of current ST use was 3.1 percent in 2016. The trend among this age group was stable through 2014. The estimates since 2014 suggest the prevalence remains stable.

Figure 6.4-1: Past 30-Day 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
Notes:
2015-16 and prior years data are not comparable due to the inclusion of snus in the definition of ST. Before 2015, smokeless tobacco included chewing tobacco or snuff/dip. In 2015 and 16, smokeless tobacco includes snuff, dip, chewing tobacco and snus.
*Denotes a statistically significant difference between this estimate and the 2014 estimate at the .05 level. Significance is indicated only for years 2002 to 2014.

Results from other national surveys with longer historical trends show that ST use among youth has declined significantly since the mid-1990s. For example, according to the Monitoring the Future study, the prevalence of past 30-day ST use among 12th graders declined from 12.2% in 1995 to 4.9% in 2017 (Miech et al., 2017). Among 10th graders, the prevalence declined from 10.5% in 1994 to 3.8% in 2017. The greatest percentage decline was observed among 8th graders, declining from 7.7% in 1994 to 1.7% in 2017, representing a 78% decline.

Table 6.4-3 presents the prevalence of ST use in context with other tobacco products. Prevalence of ST use is significantly lower than the prevalence of cigarette smoking. Across tobacco products, prevalence of use is highest among young adults, compared to older adults and youth.

Table 6.4-3: Prevalence of Current Tobacco Use by Product Among Adults and Youth (PATH, Wave 1, 2013 - 2014)

Percent of Adults (18 to 24-year-olds, ≥ 25 years old) Reporting Current (Every Day or Some Days) Use of Tobacco Products			**Percent of Youth (12 to 17-year-olds) Reporting Past 30-Day Use of Tobacco Products**	
Tobacco Product	**Adults 18-24**	**Adults ≥ 25**	**Tobacco Product**	**Youth 12-17**
Any tobacco	37.6%	26.0%	Any tobacco	8.9%
Cigarettes[1]	19.6%	17.9%	Cigarettes	4.6%
Hookah	18.2%	2.1%	E-cigarettes	3.1%
Any cigar	14.1%	6.9%	Any cigar	2.5%
Cigarillos	10.7%	3.4%	Cigarillos	2.2%
E-cigarettes	8.9%	5.0%	Hookah	1.7%
Traditional cigars	5.9%	4.3%	Smokeless (including snus)	1.6%
Smokeless (including snus)	5.2%	3.1%	Smokeless (excluding snus)	1.4%
Smokeless (excluding snus)	4.6%	2.9%	Traditional cigars	0.7%
Filtered cigars	3.5%	1.8%	Snus pouches	0.5%
Pipe tobacco	2.2%	1.0%	Filtered cigars	0.5%
Snus	1.8%	0.6%	Pipe tobacco	0.3%
Dissolvable tobacco	0.2%	0.1%		

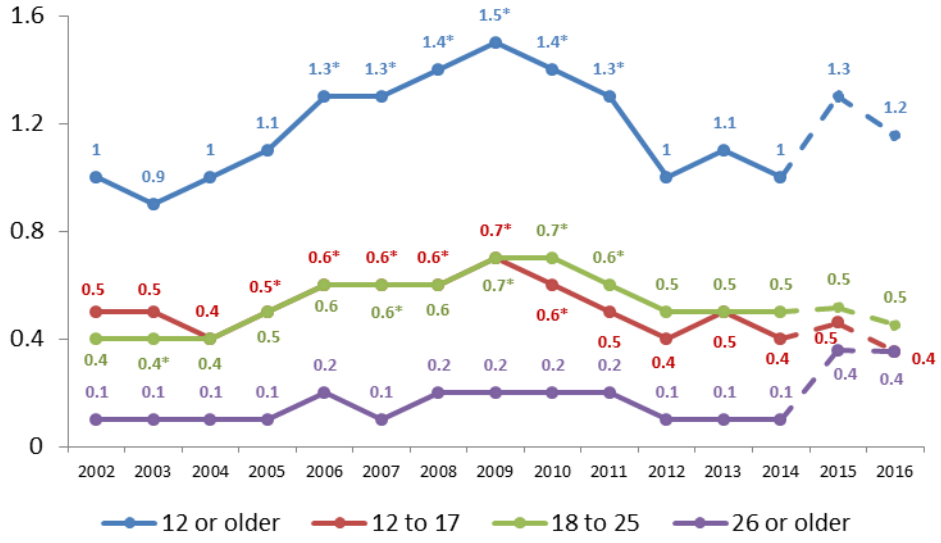
Source: Kasza, K. A., et al. (2017). Tobacco-Product Use by Adults and Youths in the United States in 2013 and 2014. *New England Journal of Medicine*, *376*(4), 342-353, Supplementary Appendix, Tables S5 and S18

[1] Definition of current use of cigarettes among adults includes the criterion of ever smoked 100 or more cigarettes.

6.4.1.2. Smokeless Tobacco Initiation

The number of recent initiates of ST in 2014, defined as those who used the product for the first time in the past year, is comparable to recorded numbers in the early 2000s (Figure 6.4-2). An upward trend in number of recent initiates peaked in 2009, followed by a corresponding downward trend through 2014. The change in the NSDUH definition of ST again constrains inferences with respect to the trend of new initiates of ST since 2014. The number of new initiates in 2015 and 2016 remained below the peak level observed in 2009.

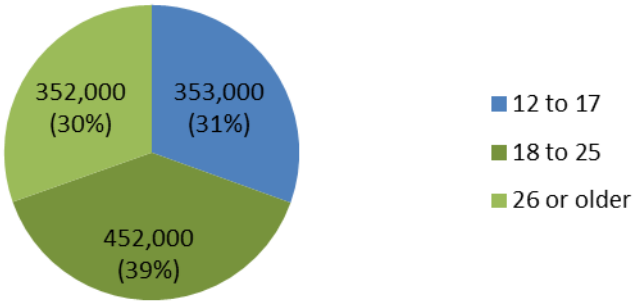
Figure 6.4-2: Past Year Smokeless Tobacco Initiates Among People Aged 12 or Older, by Age Group (in Millions), 2002-2016



Sources:
2002-2014: Reproduced from Lipari, Kroutil and Pemberton (2015). Risk and Protective Factors and Initiation of Substance Use: Results from the 2014 National Survey on Drug Use and Health; Figure 28, page 26.
2015: Lipari, Williams, Copello and Pemberton (2016). Risk and Protective Factors and Estimates of Substance Use Initiation: Results from the 2015 National Survey on Drug Use and Health; Page 17.
2016: Lipari, Ahrnsbrak, Pemberton and Porter (2017). Risk and Protective Factors and Estimates of Substance Use Initiation: Results from the 2016 National Survey on Drug Use and Health; Page 17.
Notes:
2015-16 and prior years data are not comparable due to the inclusion of snus in the definition of ST. Before 2015, smokeless tobacco included chewing tobacco or snuff/dip. In 2015 and 16, smokeless tobacco includes snuff, dip, chewing tobacco and snus.
*Denotes a statistically significant difference between this estimate and the 2014 estimate at the .05 level. Significance is indicated only for years 2002 to 2014.

Figure 6.4-3 shows the distribution of recent initiates by age category based on 2016 NSDUH data reported by Lipari et al. (2017). Approximately 69 percent of recent initiates of ST were 18 years of age or older (Figure 6.4-3).

Figure 6.4-3: Past Year Smokeless Tobacco Initiates Among People Aged 12 or Older, by Age Group, 2016



Source: Based on data reported in Lipari et al. (2017). Risk and Protective Factors and Estimates of Substance Use Initiation: Results from the 2016 National Survey on Drug Use and Health; page 17

Age of initiation of ST products varied across the studies reviewed. NSDUH provides a measure of average age of initiation defined as the age of first ever use of ST. According to this data source, among those age 12 to 49 years old who used ST for the first time in the past year, the average age of initiation has been 18 or older for well over a decade. The average age of initiation was 20.4 years in 2016 (Lipari et al., 2017) and 21.3 years in 2015 (Lipari et al., 2016). From 2002 to 2014, the average age of ST initiation ranged from a low of 18 years in 2007 to a high of 19.8 years in 2011(Lipari et al., 2015).

Based on PATH Wave 1 data collected in 2013-2014, among current established users of ST (excluding snus), the median age of first ST use, even one or two times, was 15.3 years old and 17.3 years old for starting regular use (Cheng et al., 2017). Among the studies included in the literature review (Section 7.5.3-1 and Section 7.5.3-2), age of initiation among youth and young adults ranged from 9 to 15 years old (Ary, Lichtenstein, Severson, Weissman, & Seeley, 1989; Bonaguro, Pugh, & Bonaguro, 1986; Chisick, Lee, Raker, & Williams, 1992; Liu et al., 2015; Riley, Barenie, & Myers, 1989; Spangler, Dignan, & Michielutte, 1997). Diverse factors may drive the differences between these studies and national survey results, including the propensity for studies to focus on youth populations that do not provide a broad representation of all individuals using ST. Studies that focus on youth populations do not account for nonusers at the time of assessment who may start using ST later.

6.4.1.3. Summary – Smokeless Tobacco Prevalence and Trends

ST prevalence among youth, young adults and older adults has been relatively stable for the past decade. The prevalence of underage ST use has declined significantly from its peak in the 1990's. The total number of new initiates of ST increased from the early 2000's through 2009, before returning to the prior levels. Although not directly comparable, the numbers of new initiates in more recent years remained below the 2009 peak. Average age of initiation of ST products varied across the studies reviewed. Based on current data from NSDUH, the majority of individuals who initiate ST are 18 years of age or older.

6.4.2. The Likelihood that Consumers Who Have Never Used Tobacco Products, Particularly Youth and Young Adults, Will Initiate Use of the Tobacco Product

We present information pertinent to this question separately for youth and adults. We did not conduct primary research among youth. For this subgroup, we rely on literature and national survey data to draw conclusions about the potential effect of marketing the candidate product with the proposed modified risk claim on initiation. For adults, we present findings from our research study.

6.4.2.1. Assessing Potential Effect on Initiation Among Adult Nonusers

We conducted the CCI Study (Appendix 7.3.2-1) in 2017 to assess the effect of the proposed modified risk claim on behavioral intentions for the candidate product (e.g., intentions to try, use, dual use and switch to the candidate product) among adult users and nonusers of tobacco products. Below, we briefly describe the CCI Study design (Appendix 7.3.2-1), which either used items sourced (Appendix 7.3.2-10 Item Tracking Matrix) from the literature or validated based on an internally conducted validation study. We summarize the validation study in Section 6.2.5.1; the following appendices provide further detail on item validity (Appendix 7.3.3-3 through 7.3.3-11).

Based on the results of this study, adult nonusers expressed low intentions to try and use the candidate product, and the proposed modified risk claim had no significant effect on these intentions. Thus, we expect no increase or decrease in the likelihood of initiation of candidate product use in adult nonusers.

6.4.2.1.1. Overview of the Claim Comprehension and Intentions Study

As one of its primary objectives, the CCI Study assessed changes in behavioral intentions between study participants exposed to the proposed modified risk claim and those who were not (Appendix 7.3.2-1). This study employed a quasi-experimental, pre-test/post-test design. Study participants were recruited online, through e-mail, by phone or in-person. All participants, regardless of recruiting mode, completed the study online. Participants were first assigned into one of six subgroups based on their tobacco use: adult smokers planning to quit (ASPQ), adult smokers not planning to quit (ASNPQ), dual users,[5] MST users,[6] former users and never users of tobacco products. We oversampled legal age to 24 year-old (LA-24) participants among both users and nonusers of tobacco products.

Participants were then randomly assigned to one of two conditions: Test or Control. In the Test condition, participants viewed an advertisement for the candidate product that contained the proposed modified risk claim. Participants in the Control condition viewed the same advertisement without the claim. Each advertisement included one of the four rotating, federally mandated warnings. Participants responded to behavioral intention questions before viewing the advertisement and again after they viewed it.

[5] The Dual user group included those who reported current use of cigarettes and MST.
[6] The MST user group could have reported use of other tobacco products, except cigarettes.

A total of 5,871 adults of legal age to purchase tobacco participated in the study, which included 4,927 main sample participants and a separate oversample of 944 participants who were LA-24. Nonusers reported no past 30-day use of tobacco products and comprised two of the study groups: never users (n = 802) and former users (n = 806). Never users may have tried tobacco products in the past, but reported not using them to a lifetime use criterion (e.g., 100 lifetime cigarettes). We pooled LA-24 participants from the main sample and oversample to create a sample of 804 nonusers of LA-24.

The CCI Study outcomes relevant to this section include: intention to try, intention to use, and positive affect. The following describes these outcomes:

Intention to Try. Three items measured intention to try, each asked before and after viewing the advertisement for the candidate product:

- 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?
  - To try Copenhagen® Snuff if one of your best friends were to offer Copenhagen® Snuff to you?

We measured the first item on a six-point scale, ranging from *Strongly disagree (1)* to *Strongly agree (6)*.[7] The other two items used a six-point scale, ranging from *Definitely not (1)* to *Definitely (6)*.[8] We calculated a composite score for each participant by averaging the participant's responses to the three items.

Intention to Use. Four items measured intention to use, each asked before and after viewing the advertisement for the candidate product:

- 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 six months.
- Copenhagen® Snuff will be my regular brand of snuff/dip/smokeless tobacco in the next 30 days.

We measured these items using a six-point scale, ranging from *Strongly disagree (1) to Strongly agree (6)*. We calculated a composite score for each participant by averaging the participant's responses to the four items.

Positive Affect to Try and Use. Behavioral intentions do not always translate to actual behavior (Ajzen, 1985). The positive affect to try and positive affect to use measures were developed to provide a more stringent assessment of intentions, by combining behavioral intentions with intention to purchase. The following intent to purchase question was used to construct the positive affect measures:

[7] 1=Strongly disagree, 2=Disagree, 3=Somewhat disagree, 4=Somewhat agree, 5=Agree, 6=Strongly agree
[8] 1=Definitely not, 2=Very unlikely, 3=Somewhat unlikely, 4=Somewhat likely, 5=Very likely, 6=Definitely

- Would you like to buy Copenhagen® Snuff now to use?

Response options were *Yes (1)* or *No (0)*. We used responses to this question in conjunction with each of the behavioral intention measures to calculate a proportion of participants with positive affect to try and use. Specifically, we determined respondents having a positive affect to try based on a composite intention to try score above the midpoint of the scale (i.e., > 3.5) and who responded *Yes* to the purchase intent question. We applied the same approach to those with an intention to use score above the midpoint of the scale and who responded *Yes* to the purchase intent question.

See Section 7.3.2 for full details and results of the CCI Study. See Section 6.3 for discussion of results pertaining to adult tobacco user study groups. Here, we highlight results relevant to adult nonusers.

6.4.2.1.2. Results of CCI Study: Intention to Try the Candidate Product

Nonusers in both the Test and Control conditions expressed low intention to try the candidate product. At both pre- and post-test to the advertisement, the average composite scores on intention to try were close to 1 across the nonuser groups and study conditions (Table 6.4-4). Less than 3% of participants in any nonuser study group indicated a positive affect to try the candidate product both before (pre-test) and after exposure (post-test) to the advertisement with (Test) or without the proposed modified risk claim (Control).

Table 6.4-4: Intention to Try the Candidate Product among Adult Nonusers – Mean Composite Scores and Proportions Indicating Positive Affect

		Never Users		Former Users		Nonusers LA-24[1]	
		Test	**Control**	**Test**	**Control**	**Test**	**Control**
Base Size		402	400	402	404	401	403
Intention to Try (Mean)	Pre-test	1.28	1.37	1.38	1.33	1.45	1.41
	Post-test	1.29	1.33	1.33	1.29	1.43	1.39
Positive Affect to Try	Pre-test	2.49%	2.25%	2.99%	1.73%	1.75%	2.48%
	Post-test	1.74%	2.00%	2.49%	1.73%	2.24%	1.74%

Source: Claim Comprehension and Intentions Study Report (Appendix 7.3.2-1; Table 7 and Table 59)
[1] LA-24=Legal age to purchase tobacco to age 24

Further, the modified risk claim did not affect nonusers' intentions to try the candidate product. After controlling for pre-test intentions to try, post-test intentions to try showed no statistically significant differences between the Test and Control conditions for never users ($p = 0.358$), former users ($p = 0.758$) and nonusers legal age to 24 years old ($p = 0.774$) based on analysis of covariance (ANCOVA) models (Appendix 7.3.2-1; Table 13, Table 12, and Table 15, respectively).

6.4.2.1.3. Results of CCI Study: Intention to Use the Candidate Product

Results for the intention to use measures were consistent with those observed for the intention to try measures. Nonusers in both the Test and Control conditions expressed little intention to use the candidate product. At both pre- and post-test, the average composite scores on intention to use were close to 1 across the nonuser groups and study conditions (Table 6.4-5). Less than 3% of participants in any nonuser study group indicated a positive affect to use the candidate product both before and after exposure to the advertisement with (Test) or without the proposed modified risk claim (Control).

Table 6.4-5: Intention to Use the Candidate Product among Adult Nonusers – Mean Composite Scores and Proportions Indicating Positive Affect

		Never Users		Former Users		Nonusers LA-24[1]	
		Test	Control	Test	Control	Test	Control
Base Size		402	400	402	404	401	403
Intention to Use (Mean)	Pre-test	1.26	1.30	1.30	1.30	1.37	1.34
	Post- test	1.25	1.32	1.27	1.25	1.37	1.32
Positive Affect	Pre- test	2.49%	2.25%	2.49%	1.98%	2.74%	2.73%
	Post- test	1.74%	2.00%	2.74%	1.73%	2.00%	1.74%

Source: Claim Comprehension and Intentions Study Report (Appendix 7.3.2-1; Table 16 and Table 60)
[1] LA-24=Legal age to purchase tobacco to age 24

Further, the modified risk claim did not affect nonusers' intentions to use the candidate product. After controlling for pre-test intentions to use, post-test intentions to use showed no statistically significant differences between the Test and Control conditions for never users ($p = 0.126$), former users ($p = 0.215$) and nonusers legal age to 24 years old ($p = 0.422$) based on ANCOVA models (Appendix 7.3.2-1; Table 22, Table 21, and Table 24, respectively).

6.4.2.1.4. Summary - Assessing Potential Effect on Initiation Among Adult Nonusers

We expect no increase or decrease in the likelihood of initiation of candidate product use in adult nonusers. Based on the results of the CCI Study, adult nonusers expressed low intentions to try and use the candidate product, and the proposed modified risk claim had no significant effect on these intentions. Further, low proportions of nonusers indicated positive affect to try or use the product, reinforcing the conclusion that nonusers are unlikely to initiate with the candidate product if it is marketed with the proposed modified risk claim.

6.4.2.2. Assessing Potential Effect on Initiation Among Youth

Using published literature and national survey data, we examined various lines of indirect evidence to evaluate the potential effect of marketing the candidate product with the

proposed modified risk claim on initiation among youth. These included underlying factors associated with ST use, risk perceptions, and reported brand use. We observed:

- A variety of factors influence youth initiation and use of ST, many of which are common to other risk behaviors. ST use behavior is more likely associated with personal, social, and environmental influences than with a specific tobacco product.
- Youth already perceive differences between risk associated with ST and cigarettes. A smaller proportion of youth perceive "great risk" associated with using ST than the proportion of youth who perceive the same for smoking cigarettes. Differences between the proportions have widened over time: Risk perceptions of cigarette smoking have increased, while risk perceptions of ST have decreased. Despite the differential risk perception in youth, the prevalence of ST use has remained stable. These patterns suggest that communicating the proposed modified risk claim may not have a substantial influence on ST use among youth.
- Very few youth who use ST report the use of Copenhagen® Snuff. In addition, brands appear to bear no relationship to prevalence. Reported brand use among youth who use ST has fluctuated over time, while prevalence has remained stable. These findings suggest that communicating the proposed modified risk claim *with the brand* of the candidate product is not likely to impact use among youth.

From these lines of indirect evidence, we expect no increase or decrease in the likelihood of initiation of candidate product use in youth. We intend to monitor underage use of tobacco products through our postmarket surveillance activities (Section 8.1).

6.4.2.2.1. Factors Associated with Smokeless Tobacco Initiation and Use Among Youth

A variety of factors have been associated with ST use among youth. In terms of demographic characteristics, the highest prevalence of ST use exists among males, whites, and those living in rural areas (Table 6.4-6).

Table 6.4-6: Prevalence of Smokeless Tobacco Use by Demographic Information, 2016

Demographic Characteristic	Percentage of 12- to 17-Year-Olds	Demographic Characteristic	Percentage of 12- to 17-Year-Olds
Total	**1.4%**	**Total**	**1.4%**
Gender		**County Type**	
Males	2.5%	Large metropolitan	1.0%
Females	0.3%	Small metropolitan	1.5%
Race/Ethnicity		Nonmetropolitan	3.0%
White	2.2%	Urbanized	1.9%

Table 6.4-6: Prevalence of Smokeless Tobacco Use by Demographic Information, 2016 (Continued)

Demographic Characteristic	Percentage of 12- to 17-Year-Olds	Demographic Characteristic	Percentage of 12- to 17-Year-Olds
Black or African American	0.3%	Less urbanized	3.3%
Hispanic or Latino	0.6%	Completely rural	6.1%
Age			
12-13	0.3%		
14-15	1.1%		
16-17	2.8%		

Source: Center for Behavioral Health Statistics and Quality. (2017). 2016 National Survey on Drug Use and Health: Detailed Tables – Table 2.29B (for Gender, Race/Ethnicity) ; Tables 2.3B, 2.4B, 2.5B (for Age); Table 2.43B (for County Type). Substance Abuse and Mental Health Services Administration, Rockville, MD.

Familial, peer-group, and role-model use of ST have been consistently reported as factors associated with trial and use. For example, ST use by a sibling has been associated with increased risk of trial and initiation of regular use (Boyle, Claxton, & Forster, 1997; Colborn, Cummings, & Michalek, 1989; Smith, Colwell, Forte, Pulczinski, & McKyer, 2015). At the same time, positive parental influences can serve as a protective factor against ST use: perceived lack of parental approval of ST use is associated with lower risk of transitioning to regular ST use (Biglan, Duncan, Ary, & Smolkowski, 1995; Bonaguro et al., 1986; Brubaker, Fowler, & Kinder, 1987; Marty, McDermott, Young, & Guyton, 1986). Peer influences and relationships have a marked effect on the likelihood of trial and initiation of regular ST use among youth. Numerous studies refer to peer use, especially use among a youth's closest friends, as having the greatest effect on ST initiation (Goebel, Crespo, Abraham, Masho, & Glover, 2000; Holman, Bricker, & Comstock, 2013; Lisnerski, McClary, Brown, Martin, & Jones, 1991).

Patterns of access to tobacco products among underage individuals should be considered in the context of social and environmental factors. The sale of tobacco products is age-restricted. Given these restrictions, the majority of underage individuals rely on social sources to access tobacco products. For example, based on our analyses of PATH wave 1 data, 38.0% of 15- to17-year-old current ST users reported usually obtaining ST by giving someone money to purchase it for them and 32.0% reported that they usually obtained ST by asking someone for it or being offered it by someone. About one in four, 23.8%, reported usually obtaining it by buying for themselves.[9] Younger and less-established tobacco users are more likely to rely on social sources than their older and more-established counterparts (Everett Jones & Caraballo, 2014; Jansen et al., 2011). An individual's social network for access to tobacco products can influence his or her tobacco use behaviors.

[9] See ALCS analyses of PATH data: Appendix 6.4-1; Table 8

Certain personality traits and related behaviors also substantially influence the risk of ST trial and initiation of regular use. For example, Holman et al. (2013) observed that peer influence, rebelliousness, and risk-seeking were strongly predictive of ST initiation in young male adolescents. Tomar and Giovino (1998) reported that in male students, risk-seeking behavior and engaging in physical fights were predictive of regular ST use, and Ebbert et al. (2006) suggested a strong association between a preference for taking legal risks and ST use.

There is evidence that various risky behaviors tend to cluster within individuals. Table 6.4-7 shows substantially higher past 30-day use of alcohol, marijuana, or tobacco products among youth who report past 30-day use of any one of these substances compared to the total sample of youth. For example, among those who report past 30-day use of ST, 57% report using alcohol, 47% report smoking, 39% report using marijuana, and 23% report smoking cigars. ST use is not unique in this regard: the pattern of elevated engagement in risky behaviors is observed for past 30-day users of the other substances as well. Furthermore, it is noteworthy that prevalence of ST use is elevated across users of the other substances, including among 17% of past 30-day users of cigars and 16% of past 30-day users of cigarettes (as compared to 2% in the entire 12- to 17-year-old population).

Table 6.4-7: Percent Reporting Past 30-Day Use of Alcohol, Marijuana, and Tobacco Products Among Individuals Reporting Past 30-Day Use of Each Individual Substance, Among 12- to 17-Year-Olds (NSDUH, 2015)

		Past 30-day use (%[1]) of				
		Alcohol	**Marijuana**	**Cigarette**	**Cigar**	**Smokeless**
Among All 12 to 17 Year Olds		**10%**	**7%**	**5%**	**2%**	**2%**
Among 12- to 17-Year-Olds Who Report Past 30-Day Use of…	**Alcohol**	100%	39%	24%	12%	9%
	Marijuana	55%	100%	35%	18%	8%
	Cigarettes	54%	56%	100%	22%	16%
	Cigars	62%	66%	50%	100%	17%
	Smokeless	57%	39%	47%	23%	100%

Source: ALCS analyses of NSDUH data for Section 6.4; Appendix 6.4-2; Table 7 through Table 12
NSDUH = National Survey on Drug Use and Health
[1] All percentages rounded to whole numbers

The associations between risky behaviors suggest common risk and protective factors underlie risky behaviors, including tobacco use (cf., Jackson et al., (2012)). While certain factors described in this section particularly apply to ST (e.g., significantly more prevalent among males), many are consistent with those identified in the published literature that pertain to cigarette smoking (cf., Turner et al. (2004)). The shared risk and protective factors for tobacco use and the observation that individuals are prone to engage in multiple risk

behaviors suggest a broader integrating framework for understanding tobacco use behavior. One theory, the common liability theory, identifies psychological and heritable factors contributing to risky behavior, substance use disorders, and problem behaviors (Hicks, Iacono, & McGue, 2012; Holman et al., 2013; Jessor & Turbin, 2014). The common liability theory uses socio-cultural and heritable cues to explain adolescent and young adult initiation into tobacco, alcohol, and other drugs, thereby constructing a general set of risk factors (Hicks et al., 2012). Consistent with this theory, with a few exceptions, the factors associated with ST use tend to not be unique to ST.

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

6.4.2.2.2. Risk and Harm Perceptions of Smokeless Tobacco Use Among Youth

With respect to risk and harm perceptions among youth, in some studies, ST users were more likely to attribute fewer negative risks or health risks to ST use in comparison to smoking (Chassin, Presson, Sherman, McLaughlin, & Gioia, 1985; Riley et al., 1989; Smith et al., 2015). This should not suggest that ST users do not perceive harm associated with use. For example, in a sample of 995 adolescent male athletes, 93.7 percent of ST users agreed that ST use is harmful to health (Creath et al., 1988).

The association between risk and harm perceptions and ST use raises the prospect that communicating reduced risk can influence increased uptake among youth. Current data provides some insights to the contrary; communicating the proposed modified risk claim may not have a substantial influence on ST use among youth.

Evidence suggests that youth currently perceive less risk and harm posed by using ST, measured in absolute terms, compared with smoking cigarettes. Our analyses of PATH wave 1 data show that 60.6% of youth 12 to 17 years of age perceive “a lot of harm” with respect to using ST, compared to 82.3% who report the same for smoking cigarettes.[10] Likewise, according to data from the Monitoring the Future (MTF) study, a smaller proportion of youth perceive “great risk” in using ST as compared with the proportion that perceive the same for smoking cigarettes (Table 6.4-8). In addition, the difference in these proportions has widened over time. For example, in 2002, 46.9% of 10th graders perceived “great risk” in using smokeless tobacco regularly versus 64.3% who perceived the same for smoking one or more packs of cigarettes (Table 6.4-8), a 17.4 percentage point difference. In 2017, the respective proportions were 40.7% and 69.8%, a 29.1 percentage point difference.

[10] See ALCS analyses of PATH data: Appendix 6.4-1; Table 9 and Table 10.

Table 6.4-8: Percentage of 8th, 10th, and 12th Graders Reporting "Great Risk" in Using Smokeless Tobacco and Smoking Cigarettes

Behavior	8th Grade		10th Grade		12th Grade	
	2002	2017	2002	2017	2002	2017
Use smokeless tobacco regularly	39.4%	34.8%	46.9%	40.7%	42.6%	38.4%
Smoke 1 or more packs of cigarettes per day	57.5%	62.1%	64.3%	69.8%	74.2%	74.9%
Smoke 1 to 5 cigarettes per day	32.8%	41.9%	35.1%	50.0%	NA	NA

Source: Miech, R. A., Schulenberg, J. E., Johnston, L. D., Bachman, J. G., O'Malley, P. M., & Patrick, M. E. (December 14, 2017). "National Adolescent Drug Trends in 2017: Findings Released." Monitoring the Future: Ann Arbor, MI. Retrieved 12/17/2017 from http://www.monitoringthefuture.org (Tables 5 to 7) (Miech et al., 2017).
NA – "not asked"

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

These data provide insight into the potential effect of marketing the candidate product with the proposed modified risk claim. Smaller proportions of youth perceive "great risk" associated with using ST than proportions who perceive the same for smoking cigarettes, and differences between the proportions have widened over time. Risk perceptions of ST have declined, while the prevalence of ST use among youth has remained generally stable. These patterns suggest that communicating the proposed modified risk claim may not have a substantial influence on ST use among youth.

6.4.2.2.3. Reported Brand Use Among Youth

Inclusion of the proposed modified risk claim with a specific tobacco brand raises the prospect that the brand can influence increased uptake among youth. Again, current data provide some insights regarding this topic. The NSDUH assessed ST brand used most often among past 30-day ST users through 2014. Table 6.4-9 shows the prevalence of past 30-day ST use among 12 to 17-year-olds. It also indicates the three ST brands that the largest proportions of past 30-day ST users in the age category reported using most often.

The ST brand cited as the brand used most often by the largest proportion of past 30-day ST users fluctuated over the years (Table 6.4-9). At the same time, overall prevalence of ST use among 12- to 17-year-olds has remained stable.

Available data suggests that very few youth who use ST report use of Copenhagen® Snuff, the product that includes the brand and form of the candidate product.[11] Based on our

[11] Copenhagen® Snuff Fine Cut currently sold in the marketplace is the provisional version of the grandfathered candidate product.

analyses of PATH wave 1 (2013-2014) data[12], 1.5% of 12 to-17-year-old past 30-day, "non-light"[13] ST users report Copenhagen® Snuff as their usual brand.[14]

These finding suggest that communicating the proposed modified risk claim *with the brand* of the candidate product is not likely to impact use among youth.

Table 6.4-9: Prevalence of Past 30-Day Smokeless Tobacco Use and Brands That Past 30-Day Smokeless Tobacco Users Cite Using Most Often During the Past 30 Days[1], Among 12- to 17-Year-Olds

Year	Prevalence of Past 30-Day ST Use	Brand Cited Most Often	Brand Cited 2nd Most Often	Brand Cited 3rd Most Often
2002	2.0%	Skoal	Copenhagen	Red Man
2003	2.0%	Skoal	Copenhagen	Red Man
2004	2.3%	Skoal	Copenhagen	Grizzly
2005	2.1%	Skoal	Grizzly	Copenhagen
2006	2.4%	Skoal	Grizzly	Copenhagen
2007	2.5%	Grizzly	Skoal	Copenhagen
2008	2.2%	Grizzly	Skoal	Copenhagen
2009	2.4%	Grizzly	Skoal	Copenhagen
2010	2.3%	Grizzly	Copenhagen	Skoal
2011	2.1%	Grizzly	Copenhagen	Skoal
2012	2.1%	Grizzly	Copenhagen	Skoal
2013	2.0%	Copenhagen	Grizzly	Red Man
2014	2.0%	Copenhagen	Grizzly	Skoal

Source: Brand use: ALCS analyses of NSDUH data: Appendix 6.4-2; Table 13
Prevalence: Behavioral Health Trends in the United States: Results from the 2014 NSDUH, page 18. (Center for Behavioral Health Statistics and Quality, 2015)
NSDUH = National Survey on Drug Use and Health
[1] Brand information for ST not collected in NSDUH after 2014.

[12] Source: ALCS analyses of PATH data: Appendix 6.4-1; Table 4
[13] Brand question only asked among "non-light" users. For youth in the PATH Study, "non-light" is defined as those who used ST on at least 10 occasions in their lifetime and used in the past 30 days.
[14] For comparison, 1.9% of 18 to 24-year-old and 9.4% of 25-year-old or older past 30-day, established ST users report Copenhagen® Snuff as their usual brand. Established ST user is defined as those who ever used ST "fairly regularly." Source: ALCS analyses of PATH data: Appendix 6.4-1, Table 11

6.4.2.2.4. Summary - Assessing Potential Effect on Initiation Among Youth

Our review of the literature and data pertaining to youth use of ST provides a basis for drawing inferences about the potential effect of marketing the candidate product with the proposed modified risk claim. From this review, we observe:

- A variety of factors influence youth initiation and use of ST, many of which are common to other risk behaviors. ST use behavior is more likely associated with personal, social, and environmental influences than with a specific tobacco product.
- Youth already perceive differences between risk associated with ST and cigarettes. A smaller proportion of youth perceive "great risk" associated with using ST than the proportion of youth who perceive the same for smoking cigarettes. Differences between the proportions have widened over time: Risk perceptions of cigarette smoking have increased, while risk perceptions of ST have decreased. Despite the differential risk perception in youth, the prevalence of ST use has remained stable. These patterns suggest that communicating the proposed modified risk claim may not have a substantial influence on ST use among youth.
- Very few youth who use ST report the use of Copenhagen® Snuff. In addition, brands appear to bear no relationship to prevalence. Reported brand use among youth who use ST has fluctuated over time, while prevalence has remained stable. These findings suggest that communicating the proposed modified risk claim *with the brand* of the candidate product is not likely to impact use among youth.

From these lines of indirect evidence, we expect no increase or decrease in the likelihood of initiation of candidate product use in youth. We intend to monitor underage use of tobacco products through our postmarket surveillance activities.

6.4.3. The Likelihood that Nonusers Who Adopt the Tobacco Product Will Switch to Other Tobacco Products That Present Higher Levels of Individual Health Risk

We provide information regarding the likelihood that marketing the candidate product with the proposed modified risk claim will result in nonusers adopting the candidate product and thereafter switching to higher risk tobacco products by focusing only on cigarettes as these present the most significant health risks and generally have the highest use prevalence relative to other tobacco products.[15]

In a premarket setting, it is difficult to ascertain whether or to what extent nonusers 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 concerning this behavior transition specific to the candidate product marketed with the proposed modified risk claim can be obtained most adequately after FDA authorization.

[15] With respect to youth, prevalence of past 30-day use of electronic cigarettes surpassed the prevalence of cigarette use among middle school and high school students in 2014 (Arrazola et al., 2015).

Notwithstanding, there is sufficient available evidence to infer the likelihood as to whether nonusers who adopt the candidate product will switch to higher risk tobacco products (i.e., cigarettes). We focus our assessment on evidence specific to the candidate product from our CCI Study and available at the ST category level drawn from published literature and national survey data. Assessing tobacco use transitions at the category level provides foundational evidence with respect to the potential impact of adoption of the candidate product and subsequent switching to cigarette smoking among nonusers. Specifically, we focused on research related to associations between ST use and subsequent cigarette smoking. Based on our assessment, we observe:

- Our CCI Study indicates that the vast majority of adult nonusers have no interest in adopting the candidate product after viewing the proposed modified risk claim. This suggests that the likelihood of adopting the candidate product and switching to cigarettes is not a relevant consideration for most nonusers.
- ST has been shown *not* to predict cigarette smoking after adjusting for factors that typically influence smoking. This is especially the case for exclusive ST use.
- The relationship between ST use and cigarette smoking is bi-directional.
- ST use has been associated with lower likelihood of smoking progression.

From these observations, we expect no increase or decrease in the likelihood that nonusers who may adopt the candidate product will switch to other tobacco products that present higher levels of individual health risk (i.e., cigarettes).

Background

The question of likelihood of adoption of the candidate product and subsequent switching to higher risk tobacco products is analogous to what Kandel (2003) refers to as the *fundamental question* in relation to the gateway hypothesis of drug involvement: "…whether prior use of a drug per se increases the risk of the use of another drug class" (p.483). The gateway hypothesis posits that drug use progresses in a sequence of stages (from licit to illicit drugs) and that the use of a drug at a lower stage in the sequence increases the risk of using a drug at a higher stage (Kandel, 1975, 2002). Although subject to debate (Vanyukov et al., 2012), the gateway paradigm has been applied in diverse spheres of public health over time (Bell & Keane, 2014), including with respect to ST use and subsequent cigarette smoking (Kozlowski, O'Connor, Edwards, & Flaherty, 2003; S. L. Tomar, 2003).

While there are associations between risky behaviors, whether engaging in a *specific risky behavior* presents a causal mechanism that acts as a "gateway" to more risky behaviors has been subject to debate among behavioral researchers and prevention practitioners.

6.4.3.1. ST Use Has Been Shown Not to Predict Cigarette Smoking After Accounting for Other Factors That Typically Influence Smoking

The existing literature relevant to the associations between ST use and subsequent cigarette smoking is conflicting. Some data indicate ST use as a positive predictor of future cigarette smoking (Haddock et al., 2001; Severson, Forrester, & Biglan, 2007; Soneji, Sargent, Tanski, & Primack, 2015; S. L. Tomar, 2003), and other data show that the relationship is not

statistically significant (Kozlowski et al., 2003; O'Connor, Flaherty, Quinio Edwards, & Kozlowski, 2003) or is diminished (O'Connor, Kozlowski, Flaherty, & Edwards, 2005) when psychosocial factors and prior cigarette use are taken into account. Consistent with these observations, Timberlake and colleagues used propensity scoring to take into account baseline differences between ST users and nonusers and found that these inherent differences account for variation in smoking outcomes (Timberlake, Huh, & Lakon, 2009). These observations suggest common liability that accounts for various risky behaviors, including ST use and cigarette smoking.

The research of Kozlowski, O'Connor and colleagues brings to light the importance of accounting for prior cigarette use when assessing associations.[16] Indeed, studies that include assessments of exclusive ever ST users at baseline (i.e., those who report only having ever used ST relative to other tobacco products) allow for stronger inferences about temporality to be drawn with respect to the question of the likelihood of nonusers adopting ST and switching to cigarette smoking.

A recent study by Watkins, Glantz and Chaffee (2018)[17] provides evidence relative to exclusive ever ST users among youth never-smokers using nationally representative PATH data. According to their findings, ever use of *ST only* at baseline was not predictive of the onset of cigarette smoking at wave 2 in the adjusted models. In addition, the associations between past 30-day ST use (with or without other non-cigarette use) at wave 1 and ever and past 30-day cigarette smoking at wave 2 were also *not* statistically significant. Various baseline risk factors for smoking remained significant in their models, and inclusion of marijuana use in sensitivity analyses reduced the magnitude of associations. These findings suggest no specific relationship linking ST use with smoking onset and are in line with the common liability model.

Analyzing four waves of the National Longitudinal Study of Adolescent Health, Kaufman and colleagues estimated transition probabilities for cigarette and ST use among a cohort of 7^{th}-12^{th} grades into young adulthood (Kaufman, Land, Parascandola, Augustson, & Backinger, 2015). Among those who reported using *ST only* (past 30-day use, exclusive of cigarette smoking) at a given time point, the estimated probability of transitioning to cigarette smoking over a 1-year period was 4.6%, which was less than the 5.6% probability among those using neither ST nor cigarettes. A similar pattern was observed among White males: The probability of transitioning to cigarette smoking over one year among those who used *ST only* at a given point in time was 6.5%, which was less than 7.8% among those using neither

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

[17] Due to the recent timing of this publication, it was not included in the literature review presented in Section 7.5.3-1 and 7.5.3-2.

product. Consistent with Watkins et al. (2018), these results show that those reporting *ST only* at a given time point were *not* more likely to report smoking at follow-up compared to users of neither ST nor cigarettes. Results of these studies run counter to gateway concerns.

6.4.3.2. The Relationship Between ST Use and Cigarette Smoking is Bi-Directional

With respect to the specificity of the relationship between ST use and cigarette smoking, some researchers investigated the bi-directional transitions between ST use and cigarette smoking. Their data show that the "ST use-cigarette smoking" transitions are bi-directional, rather than unidirectional. Chang, Levy, and Meza, (2017)[18] analyzed ST use and cigarette smoking transitions from 2010 to 2011 using the Tobacco Use Supplement of the Current Population Survey (TUS-CPS). The proportion of males (age 15 or older) who switched from ST to cigarettes (1.4%) reported in their study was comparable to the proportion who switched from cigarettes to ST (1.2%). In their study following youth into young adulthood, Kaufman et al. (2015) report higher probabilities of transitioning from ST to cigarettes than from cigarettes to ST, but noted that this finding was not surprising due to the higher prevalence of cigarette smoking. These observations also raise the importance of inspecting associations between cigarette smoking and subsequent ST use, the opposing gateway sequence.

Secondary analyses to explore bi-directional associations. To further elucidate this issue, we analyzed PATH wave 1 and 2 data to assess whether exclusive ever:

a. ST use predicts the onset of cigarette smoking and examine whether exclusive ST users contribute to a significant amount of new smokers, and
b. cigarette use predicts the onset of ST use, and examine whether exclusive cigarette smokers contribute to a significant amount of new ST users.

We focused our analyses on youth 12 to 17 years of age at both waves. We based our assessment of the relationship between ST use and the onset of cigarette smoking on the population of individuals who reported never smoking at wave 1 (n=8,608). Exclusive ever ST users were defined as those who reported only ever using ST[19] at wave 1. Additional comparison groups included those who reported ever use of ST and at least one other tobacco product, ever use of another tobacco product(s) but not ST, and never use of any tobacco product at wave 1. Cigarette onset was measured as ever use of cigarettes at wave 2. More specifically, we computed the incidence of those who reported ever use of cigarettes for the first time in wave 2 among never cigarette smokers at wave 1. Details of our analyses and results are included in Appendix 6.4-1.

When assessing the relationship between cigarette smoking and the onset of ST use, we based the analyses on the population of individuals who reported never using ST at wave 1 (n=9,143). Exclusive ever cigarette smokers were defined as those who reported only ever smoking cigarettes at wave 1. Additional comparison groups included those who reported ever use of cigarettes and at least one other tobacco product, ever use of another tobacco(s) product but not cigarettes, and never use of any tobacco product at wave 1. Onset was

[18] Due to the recent timing of this publication, it was not included in the literature review presented in Section 7.5.3-2.
[19] ST excluded snus

measured as ever use of ST at wave 2: We computed the incidence of those who reported ever use of ST for the first time in wave 2 among never ST users at wave 1.

We focus our discussion of results on exclusive ever ST and cigarette users in comparison to never users of tobacco products.

Secondary analyses - results. Our analyses show the risk of smoking onset at wave 2 among exclusive ST users at wave 1 was not statistically different than the risk among youth who had not used any tobacco products (incidence of cigarette onset was 7.3% among exclusive ST users and 3.0% among never users at baseline; OR=2.5, p=0.171) (Table 6.4-10).

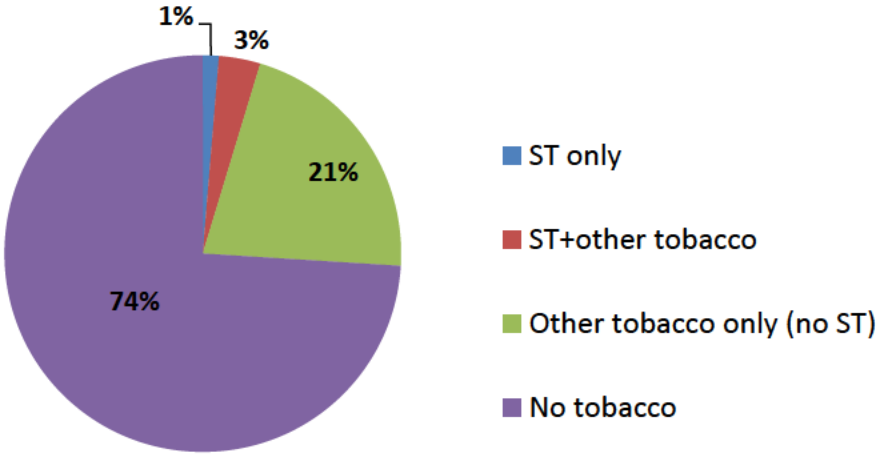
Table 6.4-10: Incidence of Cigarette Onset at Wave 2 Among Never Smokers Age 12-17 Years Old at Wave 1 - Data from PATH (n=8,608)

Wave 1 Ever Use Status		Incidence of Cigarette Smoking[1] at Wave 2	
	n	% (95% CI)	OR (95% CI)
Exclusive ST	59	7.3 (2.3,20.9)	2.5 (0.7, 9.7)
ST+ other tobacco	41	22.7 (12.9,36.9)	**9.5 (4.5, 20.0)**
Other tobacco, no ST	511	13.6 (10.6,17.2)	**5.1 (3.6, 7.1)**
No tobacco	7997	3.0 (2.6,3.4)	Reference

Source: ALCS analyses of PATH data for Section 6.4, Appendix 6.4-1; Table 12-1 and Table 12-2.
ST = Smokeless Tobacco
Other tobacco products include cigars, hookah, pipe, bidi, kretek, snus, dissolvable tobacco, and e-cigarettes.
Notes: Bold font indicates statistical significance at 0.05 level.
[1] Number of new ever smokers at wave 2 divided by the number of never smokers at wave 1.

Exclusive ever ST users at wave 1 represented 1% new cigarette smokers at wave 2 (Figure 6.4-4). The largest proportion (74%) of new cigarette smokers at wave 2 was never tobacco users at wave 1.

Figure 6.4-4: Composition of New Cigarette Smokers[1] Age 12-17-Years-Old at Wave 2 Based on Ever Smokeless Tobacco and Other Tobacco Use Status at Wave 1 (%) (n=325)



Source: ALCS analyses of PATH data for Section 6.4; Appendix 6.4-1; Table 12-3
ST: smokeless tobacco
Other tobacco products include cigars, hookah, pipe, bidi, kretek, snus, dissolvable tobacco, and e-cigarettes.
Percentages do not add to 100% due to rounding.
[1]Defined as reporting ever use of cigarettes for first time at Wave 2

With respect to the transition from cigarette smoking to ST use, our analyses show the risk for ST use onset at wave 2 among exclusive cigarette smokers at wave 1 was statistically greater than the risk among youth who had not used any tobacco products (incidence of ST use was 7.7% among exclusive cigarette smokers and 1.0% among never users at baseline; OR=8.0, $p<0.05$) (Table 6.4-11).

Table 6.4-11: Incidence of Smokeless Tobacco Onset at Wave 2 Among Never Smokeless Tobacco Users Age 12-17 Years Old at Wave 1 - Data from PATH (n=9,143)

Wave 1 Ever Use Status		Incidence of ST Use[1] at Wave 2	
	n	% (95% CI)	OR (95% CI)
Exclusive cigarettes	280	7.7 (5.1,11.4)	**8.0 (4.8, 13.1)**
Cigarettes+ other tobacco	484	4.9 (3.0,7.8)	**4.9 (2.6, 9.2)**
Other tobacco	506	4.3 (2.5,7.5)	**4.3 (2.2, 8.5)**
No tobacco	7873	1.0 (0.8,1.3)	Reference

Source: ALCS Analyses of PATH Data, Appendix 6.4-1; Table 13-1 and Table 13-2
ST = Smokeless Tobacco
Other tobacco products include cigars, hookah, pipe, bidi, kretek, snus, dissolvable tobacco, and e-cigarettes.
Notes: Bold font indicates statistical significance at 0.05 level
[1] Number of new ever ST users at wave 2 divided by the number of never ST users at wave 1.

Exclusive ever cigarette smokers at wave 1 represented 14% new ST users at wave 2 (Appendix 6.4-1; Table 13-3). The largest proportion (55%) of new ST users at wave 2 was never tobacco users at wave 1.

Secondary analyses – summary. Our analyses show that the risk for cigarette smoking at wave 2 among exclusive ever ST users at baseline is on par with the risk for ST use at wave 2 among exclusive ever cigarette smokers at baseline.[20] The cigarette smoking-to-ST use association was statistically significant; whereas, the ST use-to-cigarette smoking association was not. The lack of evidence for the ST use-to-cigarette smoking relationship and the robust cigarette smoking-to-ST use relationship does not support the notion that ST plays a specific role in smoking onset.

6.4.3.3. ST Use Has Been Associated with Lower Likelihood of Smoking Progression

Some studies reviewed provide insight relative to use of ST and smoking progression. Pooling three years of National Survey on Drug Use and Health cross-sectional data for white men and boys, Rodu & Cole (2010) found that ST initiators were significantly less likely than cigarette initiators to report current smoking. Wang et al. (2016) pooled data from three waves of Tobacco Use Supplement of the Current Population Survey (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. As described earlier, Kaufman et al. (2015) found that probabilities to transition to cigarettes was lower among exclusive ST users compared to nonusers of either tobacco product. In addition, these researchers also report that the probability of transitioning to no use of cigarettes and ST was about twice as high among exclusive ST users compared to exclusive cigarette smokers.

6.4.3.4. Summary – Likelihood of Adopting the Product and Switching to Cigarettes

Our literature review, analysis of national survey data, and CCI Study findings provide a basis to infer the impact of marketing the candidate product with the proposed modified risk claim on adoption of the product and switching to cigarette smoking among nonusers. Based on our assessment, we observe:

- Our CCI Study indicates that the vast majority of adult nonusers have no interest in adopting the candidate product after viewing the proposed modified risk claim. This suggests that the likelihood of adopting the candidate product and switching to cigarettes is not a relevant consideration for most nonusers.
- ST has been shown *not* to predict cigarette smoking after adjusting for factors that typically influence smoking. This is especially the case for exclusive ST use.
- The relationship between ST use and cigarette smoking is bi-directional.
- ST use has been associated with lower likelihood of smoking progression.

[20] A similar result has been observed in the literature examining the association between electronic cigarette use and subsequent use of combustible tobacco products (Leventhal et al., 2015); full text and supplemental tables).

From these observations, we expect no increase or decrease in the likelihood that nonusers who may adopt the candidate product will switch to other tobacco products that present higher levels of individual health risk (i.e., cigarettes).

Direct evidence regarding nonusers adopting the candidate product and switching to cigarettes if the candidate product is marketed with the proposed modified risk claim can be obtained most adequately after FDA authorization. We will monitor use behavior in nonusers in our postmarket surveillance activities.

6.4.4. The Likelihood that Former Users of Tobacco Products Will Reinitiate Use with the Tobacco Product

As presented in Section 6.4.2.1.2, former tobacco users expressed low intentions to try and use the candidate product, and the modified risk claim did not significantly impact these intentions. The published literature on this behavior pattern is sparse (Section 7.5.3-1 and 7.5.3-2).

The effect of the proposed modified risk claim under real-world conditions for this and the other questions addressed in this section will be best assessed by postmarket surveillance.

6.4.5. Conclusions

Based on the results of our study, a comprehensive review of the literature, and analyses of national survey data, we conclude:

- Evidence from the CCI Study indicates no increase or decrease in the likelihood that adult nonusers will initiate use of the candidate product. Adult nonusers express low intentions to try and use the candidate product, and we observed no differences on these measures between those who were exposed to an advertisement with the proposed modified risk claim and those who were exposed to the same advertisement without the claim.
- We expect no increase or decrease in the likelihood that youth will initiate use of the candidate product, based on our assessment of lines of indirect evidence. A variety of factors influences youth use of ST (e.g., peer influences), and the proposed modified risk claim is unlikely to change these factors.
- We expect no increase or decrease in the likelihood that nonusers who may adopt the candidate product will switch to other tobacco products that present higher levels of individual health risk (i.e., cigarettes). ST has been shown *not* to predict cigarette smoking after adjusting for factors that typically influence smoking. Adult nonusers express little interest in adopting the candidate product; thus, this transition is not a relevant consideration for most nonusers.
- Evidence from the CCI Study indicates no increase or decrease in the likelihood that former users of tobacco will reinitiate use with the candidate product. Adult former tobacco users express low intentions to try and use the candidate product, and we observed no differences on these measures between those who were exposed to an advertisement with the proposed modified risk claim and those who were exposed to the same advertisement without the claim.

Overall, we anticipate minimal unintended consequences of marketing the candidate product with the proposed modified risk claim among nonusers. Finally, we intend to monitor use behavior in nonusers through postmarket surveillance activities (see Section 8.1).

6.4.6. Literature Cited

Ajzen, I. (1985). From Intentions to Actions: A Theory of Planned Behavior *Action Control*: Springer, Berlin, Heidelberg.

Arrazola, R. A., Singh, T., Corey, C. G., Husten, C. G., Neff, L. J., Apelberg, B. J., . . . Caraballo, R. S. (2015). Tobacco use among middle and high school students - United States, 2011-2014. *MMWR. Morbidity and mortality weekly report, 64*(14), 381-385.

Ary, D. V., Lichtenstein, E., Severson, H., Weissman, W., & Seeley, J. R. (1989). An in-depth analysis of male adolescent smokeless tobacco users: interviews with users and their fathers. *Journal of behavioral medicine, 12*(5), 449-467.

Bell, K., & Keane, H. (2014). All gates lead to smoking: the 'gateway theory', e-cigarettes and the remaking of nicotine. *Soc Sci Med, 119*, 45-52. doi:10.1016/j.socscimed.2014.08.016

Biglan, A., Duncan, T. E., Ary, D. V., & Smolkowski, K. (1995). Peer and parental influences on adolescent tobacco use. *Journal of behavioral medicine, 18*(4), 315-330.

Bonaguro, J. A., Pugh, M., & Bonaguro, E. W. (1986). Multivariate analysis of smokeless tobacco use by adolescents in grades four through twelve. *Health education, 17*(2), 4-7.

Boyle, R. G., Claxton, A. J., & Forster, J. L. (1997). The role of social influences and tobacco availability on adolescent smokeless tobacco use. *Journal of adolescent health care, 20*(4), 279-285.

Brubaker, R. G., Fowler, C., & Kinder, B. N. (1987). Parental influence on adolescents' intention to use smokeless tobacco. *Health education research, 2*(4), 409-416.

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

Chassin, L., Presson, C., Sherman, S. J., McLaughlin, L., & Gioia, D. (1985). Psychosocial correlates of adolescent smokeless tobacco use. *Addictive behaviors, 10*(4), 431-435.

Cheng, Y. C., Rostron, B. L., Day, H. R., Stanton, C. A., Hull, L. C., Persoskie, A., . . . Borek, N. (2017). Patterns of Use of Smokeless Tobacco in US Adults, 2013-2014. *Am J Public Health, 107*(9), 1508-1514. doi:10.2105/ajph.2017.303921

Chisick, M. C., Lee, S., Raker, T., & Williams, T. R. (1992). A profile of tobacco use among teenage dependents. *Military medicine, 157*(7), 354-357.

Colborn, J. W., Cummings, K. M., & Michalek, A. M. (1989). Correlates of adolescents' use of smokeless tobacco. *Health education quarterly, 16*(1), 91-100.

Creath, C. J., Shelton, W. O., Wright, J. T., Bradley, D. H., Feinstein, R. A., & Wisniewski, J. F. (1988). The prevalence of smokeless tobacco use among adolescent male athletes. *Journal of the American Dental Association, 116*(1), 43-48.

Ebbert, J. O., Haddock, C. K., Vander, W. M., Klesges, R. C., Poston Walker, S. C., & Debon, M. (2006). Predictors of smokeless tobacco initiation in a young adult military cohort. *American journal of health behavior, 30*(1), 103-112.

Everett Jones, S., & Caraballo, R. S. (2014). Usual source of cigarettes and alcohol among US high school students. *J Sch Health, 84*(8), 493-501. doi:10.1111/josh.12174

Goebel, L. J., Crespo, R. D., Abraham, R. T., Masho, S. W., & Glover, E. D. (2000). Correlates of youth smokeless tobacco use. *Nicotine & tobacco research, 2*(4), 319-325.

Haddock, C. K., Weg, M. V., DeBon, M., Klesges, R. C., Talcott, G. W., Lando, H., & Peterson, A. (2001). Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males. *Preventive medicine, 32*(3), 262-267.

Hicks, B. M., Iacono, W. G., & McGue, M. (2012). Index of the transmissible common liability to addiction: Heritability and prospective associations with substance abuse and related outcomes. *Drug and alcohol dependence, 123, Supplement 1*, S18-S23.

Holman, L. R., Bricker, J. B., & Comstock, B. A. (2013). Psychological predictors of male smokeless tobacco use initiation and cessation: a 16-year longitudinal study. *Addiction (Abingdon, England), 108*(7), 1327-1335.

Jackson, C. A., Henderson, M., Frank, J. W., & Haw, S. J. (2012). An overview of prevention of multiple risk behaviour in adolescence and young adulthood. *J Public Health (Oxf), 34 Suppl 1*, i31-40. doi:10.1093/pubmed/fdr113

Jansen, P., Toomey, T. L., Nelson, T. F., Fabian, L. E., Lenk, K. M., & Forster, J. L. (2011). Sources of cigarettes among adolescent smokers: Free or purchased? *American Journal of Health Education, 42*(3), 154-160. doi:10.1080/19325037.2011.10599182

Jessor, R., & Turbin, M. S. (2014). Parsing protection and risk for problem behavior versus pro-social behavior among US and Chinese adolescents. *J Youth Adolesc, 43*(7), 1037-1051. doi:10.1007/s10964-014-0130-y

Kandel, D. (1975). Stages in adolescent involvement in drug use. *Science, 190*(4217), 912-914. doi:10.1126/science.1188374

Kandel, D. (2002). Examining the gateway hypothesis. In D. Kandel (Ed.), *Stages and Pathways of Drug Involvement* (pp. 3-11). Cambridge: Cambridge University Press.

Kandel, D. (2003). Does marijuana use cause the use of other drugs? *JAMA, 289*(4), 482-483.

Kasza, K. A., Ambrose, B. K., Conway, K. P., Borek, N., Taylor, K., Goniewicz, M. L., . . . Hyland, A. J. (2017). Tobacco-Product Use by Adults and Youths in the United States in 2013 and 2014. *New England journal of medicine, 376*(4), 342-353. doi:10.1056/NEJMsa1607538

Kaufman, A. R., Land, S., Parascandola, M., Augustson, E., & Backinger, C. L. (2015). Tobacco use transitions in the United States: The National Longitudinal Study of Adolescent Health. *Preventive medicine, 81*, 251-257. doi:10.1016/j.ypmed.2015.08.026

Kozlowski, L. T., O'Connor, R. J., Edwards, B. Q., & Flaherty, B. P. (2003). Most smokeless tobacco use is not a causal gateway to cigarettes: using order of product use to evaluate causation in a national US sample. *Addiction, 98*(8), 1077-1085.

Leventhal, A. M., Strong, D. R., Kirkpatrick, M. G., Unger, J. B., Sussman, S., Riggs, N. R., . . . Audrain-McGovern, J. (2015). Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA, 314*(7), 700-707. doi:10.1001/jama.2015.8950

Lipari, R. N., Ahrnsbrak, R. D., Pemberton, M. R., & Porter, J. D. (2017). Risk and protective factors and estimates of substance use initiation: Results from the 2016 National Survey on Drug Use and Health. Retrieved from https://www.samhsa.gov/data/sites/default/files/NSDUH-DR-FFR3-2016/NSDUH-DR-FFR3-2016.htm

Lipari, R. N., Kroutil, L., & Pemberton, M. (2015). Risk and Protective Factors and Initiation of Substance Use: Results from the 2014 National Survey on Drug Use and Health. Retrieved from http://www.samhsa.gov/data/sites/default/files/NSDUH-DR-FRR4-2014rev/NSDUH-DR-FRR4-2014.pdf

Lipari, R. N., Williams, M. R., Copello, E. A. P., & Pemberton, M. R. (2016). Risk and protective factors and estimates of substance use initiation: Results from the 2015 National Survey on Drug Use and Health. Retrieved from https://www.samhsa.gov/data/sites/default/files/NSDUH-PreventionandInit-2015/NSDUH-PreventionandInit-2015.htm

Lisnerski, D. D., McClary, C. L., Brown, T. L., Martin, J. P., & Jones, D. R. (1991). Demographic and predictive correlates of smokeless tobacco use in elementary school children. *American journal of health promotion, 5*(6), 426-431.

Liu, S. T., Nemeth, J. M., Klein, E. G., Ferketich, A. K., Kwan, M.-P., & Wewers, M. E. (2015). Risk perceptions of smokeless tobacco among adolescent and adult users and nonusers. *Journal of health communication, 20*(5), 599-606. doi:10.1080/10810730.2015.1012237

Marty, P. J., McDermott, R. J., Young, M., & Guyton, R. (1986). Prevalence and psychosocial correlates of dipping and chewing behavior in a group of rural high school students. *Health education, 17*(2), 28-31.

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.orgJohnston

O'Connor, R. J., Flaherty, B. P., Quinio Edwards, B., & Kozlowski, L. T. (2003). Regular smokeless tobacco use is not a reliable predictor of smoking onset when psychosocial predictors are included in the model. *Nicotine &Tobacco Research, 5*(4), 535-543.

O'Connor, R. J., Kozlowski, L. T., Flaherty, B. P., & Edwards, B. Q. (2005). Most smokeless tobacco use does not cause cigarette smoking: results from the 2000 National Household Survey on Drug Abuse. *Addictive behaviors, 30*(2), 325-336.

Riley, W. T., Barenie, J. T., & Myers, D. R. (1989). Typology and correlates of smokeless tobacco use. *Journal of adolescent health care, 10*(5), 357-362.

Rodu, B., & Cole, P. (2010). Evidence against a gateway from smokeless tobacco use to smoking. *Nicotine &Tobacco Research, 12*(5), 530-534.

Severson, H., Forrester, K. K., & Biglan, A. (2007). Use of smokeless tobacco is a risk factor for cigarette smoking. *Nicotine & tobacco research, 9*(12), 1331-1337.

Smith, M. L., Colwell, B., Forte, C. A., Pulczinski, J. C., & McKyer, E. L. (2015). Psychosocial Correlates of Smokeless Tobacco Use Among Indiana Adolescents. *Journal of community health, 40*(2), 208-214.

Soneji, S., Sargent, J. D., Tanski, S. E., & Primack, B. A. (2015). Associations between initial water pipe tobacco smoking and snus use and subsequent cigarette smoking: results from a longitudinal study of US adolescents and young adults. *JAMA pediatrics, 169*(2), 129-136. doi:10.1001/jamapediatrics.2014.2697

Spangler, J. G., Dignan, M. B., & Michielutte, R. (1997). Correlates of tobacco use among Native American women in western North Carolina. *American journal of public health, 87*(1), 108-111.

Timberlake, D. S., Huh, J., & Lakon, C. M. (2009). Use of propensity score matching in evaluating smokeless tobacco as a gateway to smoking. *Nicotine & tobacco research, 11*(4), 455-462.

Tomar, S. L. (2003). Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. experience. *Nicotine & tobacco research, 5*(4), 561-569.

Tomar, S. L., & Giovino, G. A. (1998). Incidence and predictors of smokeless tobacco use among US youth. *American journal of public health, 88*(1), 20-26.

Turner, L., Mermelstein, R., & Flay, B. (2004). Individual and contextual influences on adolescent smoking. *The Annals of the New York Academy of Sciences, 1021*, 175-197. doi:10.1196/annals.1308.023

Vanyukov, M. M., Tarter, R. E., Kirillova, G. P., Kirisci, L., Reynolds, M. D., Kreek, M. J., . . . Ridenour, T. A. (2012). Common liability to addiction and "gateway hypothesis": theoretical, empirical and evolutionary perspective. *Drug Alcohol Depend, 123 Suppl 1*, S3-17. doi:10.1016/j.drugalcdep.2011.12.018

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

Watkins, S. L., Glantz, S. A., & Chaffee, B. W. (2018). Association of Noncigarette Tobacco Product Use With Future Cigarette Smoking Among Youth in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2015. *JAMA Pediatr*. doi:10.1001/jamapediatrics.2017.4173