6.3.: EFFECT OF THE PRODUCT ON TOBACCO USE BEHAVIOR AMONG CURRENT TOBACCO USERS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

6.3.   EFFECT OF THE PRODUCT ON TOBACCO USE BEHAVIOR AMONG CURRENT TOBACCO USERS

6.3.1.   Introduction

The U.S. Food, Drug and Cosmetic Act (FDCA) §911(d)(6) requires that an MRTPA include "data and information on how consumers actually use the tobacco product." Additionally, FDA requests in its 2012 Draft MRTPA Guidance that an application contain evidence needed to evaluate the impact of marketing the modified risk tobacco product on current tobacco users, including:

- the likelihood that current tobacco product users will start using the product;

- the likelihood that tobacco users who adopt the product will switch to or switch back to other tobacco products that present higher levels of individual health risk;

- the likelihood that consumers will use the product in conjunction with other tobacco products;

- the likelihood that users who may have otherwise quit using tobacco products, will instead use the product; and

- the likelihood that consumers will use the product as intended or designed.

To assess the full effect that an MRTP and its marketing may have on population health, FDA recommends that applicants submit human study data characterizing abuse liability.[1]

This section will address the topics raised by FDA using information obtained from primary research using the candidate product[2] and through review of the published literature on smokeless tobacco (ST) product use (Section 7.5.2-1 and 7.5.2-2). We note that although much of the published literature does not include data for specific products, we consider the results of ST studies in general to be relevant to FDA's questions relating to the behaviors among current tobacco users.

Overall, our study among tobacco product users suggested only minimal changes in product use behavior after seeing our proposed modified risk claim. Yet, a focus on reducing tobacco-related morbidity and mortality among the population of adults who continue to use tobacco products must include providing accurate information about their risks to encourage

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[1] According to the MRTPA draft guidance document: "Abuse liability is the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product. Physical dependence is characterized by the development of tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping use of the tobacco product. Psychological dependence is characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain consistently."

[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.

behavior change. Acknowledging the health risks of tobacco products and informing adult smokers (AS) 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 result in beneficial public health outcomes. In fact, Sweden has the lowest male lung cancer death rates compared to other European countries. Since the 1990s, Swedish cigarette sales declined and ST use increased, resulting in a daily smoking rate of 5% in 2017 (Rodu & Cole, 2009). USSTC is committed to making lower risk products available to consumers and pursuing FDA authorization to provide consumers with accurate and non-misleading information about their lower health risks.

6.3.2. How Complex Tobacco Product Use Beliefs and Behaviors Relate to the Likelihood Questions Posed by FDA

FDA's ultimate goal in recommending that applicants include tobacco use behavior information in MRTPAs apparently is to help address the Section 911 (g)(1)(B) standard that marketing the product with a modified risk claim will "benefit the health of the population as a whole." Predicting the likelihood of change in current use behavior, however, is difficult because consumer behavior and choice of tobacco product use is often complex. Several factors influence consumers' decisions to use a tobacco product marketed with a modified risk claim, and those factors are difficult to ascertain in a pre-market setting. For example, influences of marketing and promotions; other reduced risk tobacco product options; and previously held beliefs regarding the risks of MST compared to smoking can all affect consumer behaviors and make pre-market predictions uncertain.

Despite a scientific consensus that ST products,[3] including the candidate product, are significantly lower on the continuum of risk than conventional cigarettes and that AS who switch from cigarette smoking to exclusive ST use would lower their individual health risks, many reports find that the majority of smokers do not perceive a risk differential between ST and cigarettes. (Hatsukami et al., 2007; Zeller & Hatsukami, 2009). FDA's Population Assessment of Tobacco and Health (PATH) survey corroborates this information, as more than 90% of U.S. adult smokers perceive ST products, including MST, to be about the same or more harmful than cigarettes.[4] Further, our analysis of the Health Information National Trends Survey (HINTS) conducted by the National Cancer Institute confirms this information. As illustrated in Figure 6.3-1, the vast majority of smokers (71%) and dual users (72%) do not believe that ST is less harmful than cigarettes. These observations are particularly important for dual users because, although they already use ST, they also continue to smoke, and the proposed modified risk claim could persuade some to stop smoking and switch completely to ST.

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[3] Statement refers to smokeless tobacco product types commonly used in the United States and may not apply to various smokeless tobacco types traditionally used in other parts of the world, particularly Asia and Africa.
[4] Based on Hyland et al., *Highlighted Findings from the Wave 1 of the Population Assessment of Tobacco and Health Study* presented at the 2016 Annual Meeting of the Society for Research on Nicotine and Tobacco, Chicago, Illinois.

Figure 6.3-1: Current Beliefs About the Relative Harmfulness of Cigarettes and ST
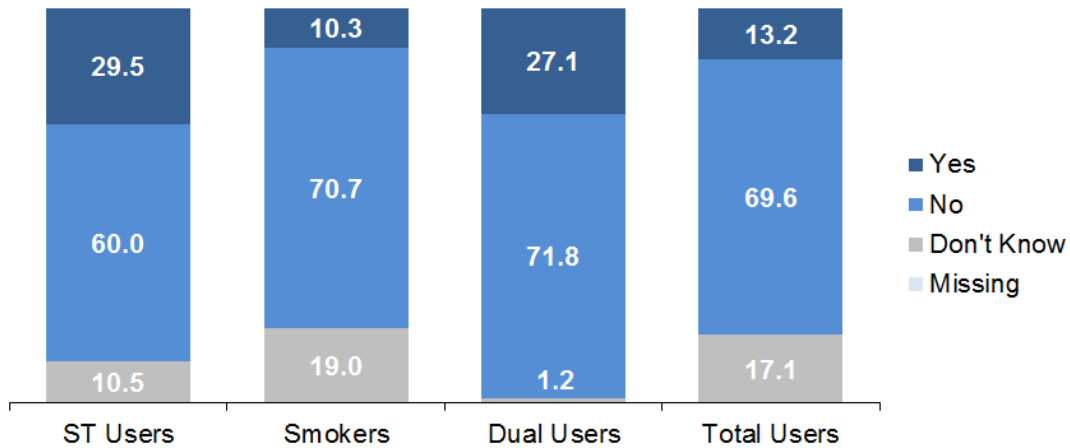
Source: Data from ALCS analysis of the 2015 National Cancer Institute Health Information National Trends Survey (HINTS)(Appendix 2.3-4). Proportions represent responses to the question: "In your opinion, do you think that some smokeless products, such as chewing tobacco, snus and snuff, are less harmful to a person's health than cigarettes?"
NOTE: Numbers may not total 100% due to rounding.

'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.

Based on publicly available data (Sept. 12, 2013-Dec. 14, 2014) from PATH Wave 1, among the approximately seven million adult ST product users, more than two million also smoke cigarettes (dual or polytobacco users). Smokers who are uninformed or misinformed about the risk differential between cigarettes and ST will likely continue to smoke cigarettes, and ST users who never receive accurate information could transition from the less harmful ST products toward the more harmful activity of cigarette smoking. There is general scientific agreement that noncombustible ST products offer lower risk than cigarettes, which is further corroborated in our review of the current scientific literature and analyses of two robust national datasets (Section 6.1). Providing information that encourages dual users to transition toward exclusive candidate product use creates a public health opportunity consistent with the intent of Section 911. Further, an accurate modified risk claim delivered to adult tobacco consumers, particularly AS or dual users who wish to stop smoking but continue to use tobacco products, could change perspectives and alter current trends. As we illustrate below, we expect this transition will take time.

6.3.3. The Likelihood That Current Tobacco Product Users[5] Will Start Using the Product

In this section we describe likelihood of initiation in *adult* tobacco consumers, primarily through our CCI Study; Section 6.4 describes our assessment of the likelihood of initiation in *youth* and *adult* non-users.

Our proposed modified risk claim is directed toward existing adult smokers. Quitting tobacco use completely will produce the most beneficial health outcomes, but for smokers unwilling to quit tobacco use, switching to ST use presents lower risk. There is relatively little published information describing the rates of ST initiation among current *adult* smokers, compared to published information regarding patterns of smoking initiation among nonusers of tobacco. One study reported that in adult males, quitting one form of tobacco and initiating another after one year was infrequent, with only 0.3% of subjects reporting initiation of regular ST use after smoking (Zhu et al., 2009).

We can establish, however, that (1) ST use is overwhelmingly a male tobacco use behavior in the U.S.; (2) many adult female cigarette smokers are averse to such products; and (3) minimal uptake, therefore, of the candidate product should be expected among women. The Centers for Disease Control and Prevention (CDC) report very low prevalence of MST use in women (fewer than one in 100 women use ST.[6] Jones et al. (2017) report that the prevalence of current ST use among adults in 2016 was predominantly younger adult males with less than a college degree, and who reside in the Midwest or West regions. As described in Section 6.4, the overall prevalence of ST use in the U.S. has been low – less than 5% – and relatively stable for over a decade (Figure 6.4-1).

6.3.3.1. CCI Study Design Overview

To assess the likelihood of use of the candidate product among current tobacco users, we asked participants in our CCI Study (Section 7.3.2) if they were likely to use the candidate product, before and after seeing the proposed claim language. Figure 6.3-2 outlines the CCI Study design.

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[5] While the term *current tobacco product users* could apply to all tobacco products, we generally limit our analysis for this and the other questions in this section to current cigarette smokers (i.e., pipes, cigars, hookah and other tobacco products were not included). Smoking represents the predominant form of tobacco use in the U.S. (Substance Abuse and Mental Health Services Administration, 2014).
[6] CDC Fact Sheet on Smokeless Tobacco Use in the United States https://www.cdc.gov/tobacco/data_statistics/fact_sheets/smokeless/use_us/index.htm (accessed on 12/2/2017)

Figure 6.3-2: Basic Outline of the Consumer Comprehension and Intentions (CCI) Study
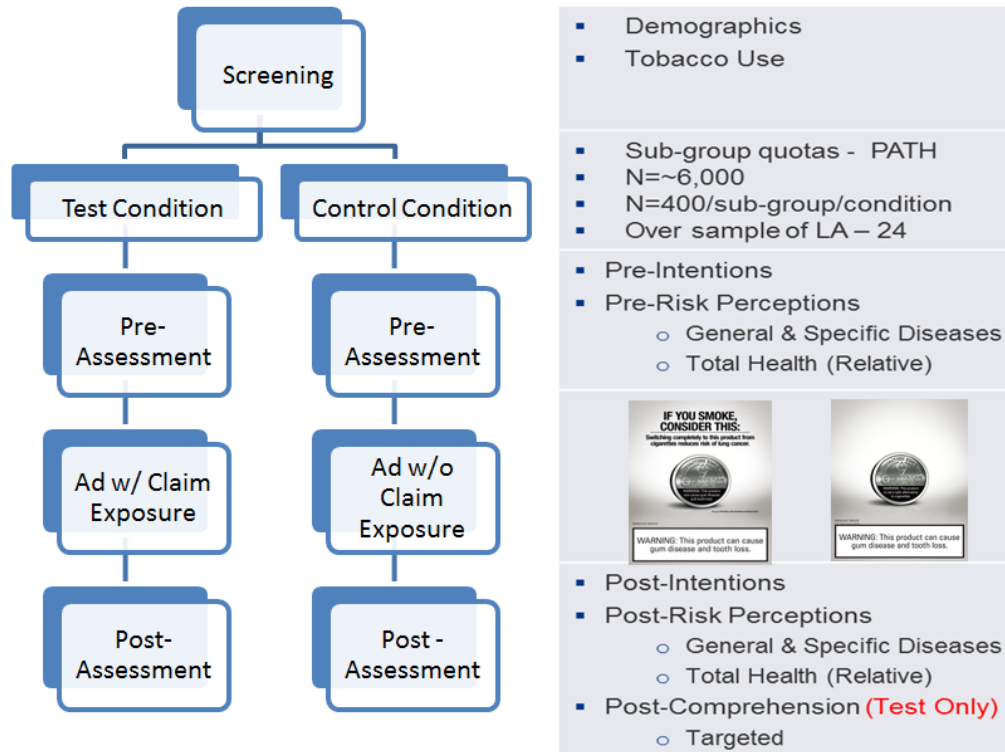
Below, we briefly describe the CCI Study design (Appendix 7.3.2-1), which either used items sourced (Appendix 7.3.2-10) from the literature or validated based on an internally conducted validation study. We summarize the validation study in Section 6.2.5.1; the following appendices provide further detail on item validity (Appendix 7.3.3-8).

This online study involved 5,871 adult (legal age to use tobacco products [LA] and older) users and nonusers of tobacco products from across the U.S., including 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. Study participants were posed questions about intentions to try the candidate product in the next 30 days, or regularly use the candidate product in the next one to six months. The study design involved comparisons of changes in behavioral intentions pre- and post- review of a single exposure to a print advertisement with the proposed modified risk claim (Test Condition) relative to the same print advertisement without the claim (Control Condition). We assessed the intent to try, use, and switch to the candidate product using a six-point scale (6=Strongly Agree, 5=Agree, 4=Somewhat Agree, 3=Somewhat Disagree, 2=Disagree, 1=Strongly Disagree). Respondents were divided into four sub-groups based on their tobacco product use behavior: adult smokers planning to quit (ASPQ), adult smokers not planning to quit (ASNPQ), MST users, and dual users.

The sample size of the CCI Study was sufficiently powered for all four sub-groups and was oversampled for an additional sub-group identified as special interest population by FDA[7] (adult users and nonusers of legal age to purchase tobacco up to 24 years of age). This study used a quasi-experimental, repeated measures design. Participants were recruited using non-probability sampling methods. Quota sampling, based on the PATH study, was used to ensure that the participants were evenly distributed between the Test and Control conditions.

We compared the Test and Control conditions on post-test intentions to try, use, dual use, and switch to the candidate product using analysis of covariance (ANCOVA) tests. We further applied logistic regression models to compare the Test and Control conditions on the intention to quit smoking and quit all tobacco. ANCOVAs and logistic regression models controlled for pre-test behavioral intentions, prior cigarette use, and prior MST use. The study did not assess factors other than the proposed claim and risk perceptions, which may influence intentions and behavior.

6.3.3.2.   CCI Study Results

As shown in Table 6.3-1, current MST or dual users showed greater overall interest in trying or using the candidate product compared to exclusive AS; however, the single exposure to the proposed claim language did not substantially change the intention to use the candidate product among any particular subgroup. Exclusive AS (either planning to quit, ASPQ or not planning to quit ASNPQ) in the study expressed minimal intention to try or use the candidate product, either before or after reading the proposed claim language. Statistical analysis of the change in intent to *try* the candidate product among AS groups and dual users showed no significant difference between the Test and Control conditions. After adjusting for covariates, the only statistically significant finding related to change in intent to *use* the candidate product occurred among ASNPQ. Specifically, ASNPQ in the Test condition reported a higher intention to *use* the candidate product after exposure than those in the Control condition, although the effect size for this difference was small (adjusted $M = 2.39$ vs. adjusted $M = 2.26$; $\eta^2 < 0.01$) (Appendix 7.3.2-1; Table 18). Inferences from these results should be assessed in the context of lack of a concomitant change in intentions to try the candidate product.

Table 6.3-1:   Composite Scores (Unadjusted Means) of Responses to Statements or Questions Related to Trial or Use of the Candidate Product Among Current Tobacco Users

Group	Condition	Intention to Try[1]		Intention to Use[1]	
		Pre	Post	Pre	Post
ASPQ	Control (n = 401)	2.43	2.30	2.31	2.20

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[7] 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).

Group	Condition	Intention to Try[1]		Intention to Use[1]	
		Pre	Post	Pre	Post
	Test (n = 406)	2.40	2.36	2.29	2.25
ASNPQ	Control (n = 403)	2.54	2.46	2.41	2.31
	Test (n = 398)	2.49	2.48	2.32	2.34*
MST users	Control (n = 341)	4.36	4.35	4.27	4.18
	Test (n = 356)	4.49	4.37	4.22	4.16
Dual Users	Control (n = 337)	4.51	4.38	4.22	4.13
	Test (n = 336)	4.59	4.54	4.43	4.32

Source: Trial - Appendix 7.3.2-1; Table 7, Use – Appendix 7.3.2-1; Table 16

ASPQ = Adult Smokers Planning to Quit, ASNPQ = Adult Smokers Not Planning to Quit, 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.)

[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 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.

We also asked participants in our CCI Study (Section 7.3.2) if they were likely to switch to the candidate product. After adjusting for covariates, we found no statistically significant differences in intentions to switch to the candidate product between the Test and Control conditions in any subgroup (Table 6.3-2). Similar findings resulted upon analysis of special subgroups including Low Health Literacy, Normal Health Literacy, or age (legal adults to 24 yrs) (sub-group data can be found in Section 7.3.2).

Table 6.3-2: Composite Scores (Unadjusted Means) of Responses to Statements or Questions Related to Switching to the Candidate Product Among Current Tobacco Users

Group	Condition	Intention to Switch[1]	
		Pre	Post
ASPQ	Control (n = 401)	2.19	2.11
	Test (n = 406)	2.16	2.11
ASNPQ	Control (n = 403)	2.08	2.06
	Test (n = 398)	2.02	2.09

Group	Condition	Intention to Switch[1]	
		Pre	Post
Dual Users	Control (n = 418)	3.33	3.27
	Test (n = 422)	3.51	3.51

Source: Appendix 7.3.2-1; Table 30
ASPQ = Adult Smokers Planning to Quit, ASNPQ = Adult Smokers Not Planning to Quit
[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 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: I plan to gradually switch from regular cigarettes to Copenhagen® Snuff. I plan on using Copenhagen® Snuff Cut as a complete replacement for regular cigarettes. I intend on switching from cigarettes to Copenhagen® Snuff in the next 6 months.

We further analyzed the response 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 expressing some interest. 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 of 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 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 (Section 2.3; Table 2.3-6). We estimated the relative percentage change in adult male smokers intending to switch to the candidate product as 20.8% (calculations shown in Appendix 7.4.2-4; Table 1). This served as input for our Population Model (Section 6.5).

We present descriptive statistics (Appendix 7.3.2-9; Table 2) on pre-test and post-test measures for responses for purchase intent ("Would you like to buy Copenhagen® Snuff now to use?"). Importantly, intent to purchase was noted among the tobacco user groups (~20% of ASPQ and ASNPQ and ~65% of current MST Users (Dual Users and MST Users)) and not among nonusers (2-3%). Furthermore, among those indicating intent to purchase, no directional changes were observed in likelihood of buying "Copenhagen Snuff if it were available" in any of the user or nonuser subgroups for the Test and Control conditions.

6.3.3.3. Contextualizing CCI Study Results Based on Cognitive Research

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.

Overview of Theory of Planned Behavior

Over 30 years of research on the TPB, originally described by Ajzen in 1985, has found three primary factors -- attitude toward the behavior, social norm and perceived behavioral control -- that lead to change in intentions and ultimately behaviors, including but not limited to change in substance use and cigarette use (Ajzen, 1985; Dohnke, Weiss-Gerlach, & Spies, 2011; Fix et al., 2017; Godin & Kok, 1996; Godin, Valois, Lepage, & Desharnais, 1992; Record, Harrington, Helme, & Savage, 2018; Schar, Gutierrez, Murphy-Hoefer, & Nelson, 2006). These factors are described as: "Attitude towards the behavior is an expression of one's positive or negative evaluation of performing a given behavior. The perceived subjective social norm reflects personal perception of the social expectations to adopt a given behavior. Perceived behavioral control reflects personal beliefs as to how easy or difficult performing the behavior is likely to be". See Figure 6.3-3 below for the schematic depiction of TPB.

Figure 6.3-3: Diagram of Ajzen's Theory of Planned Behavior (Godin & Kok, 1996)
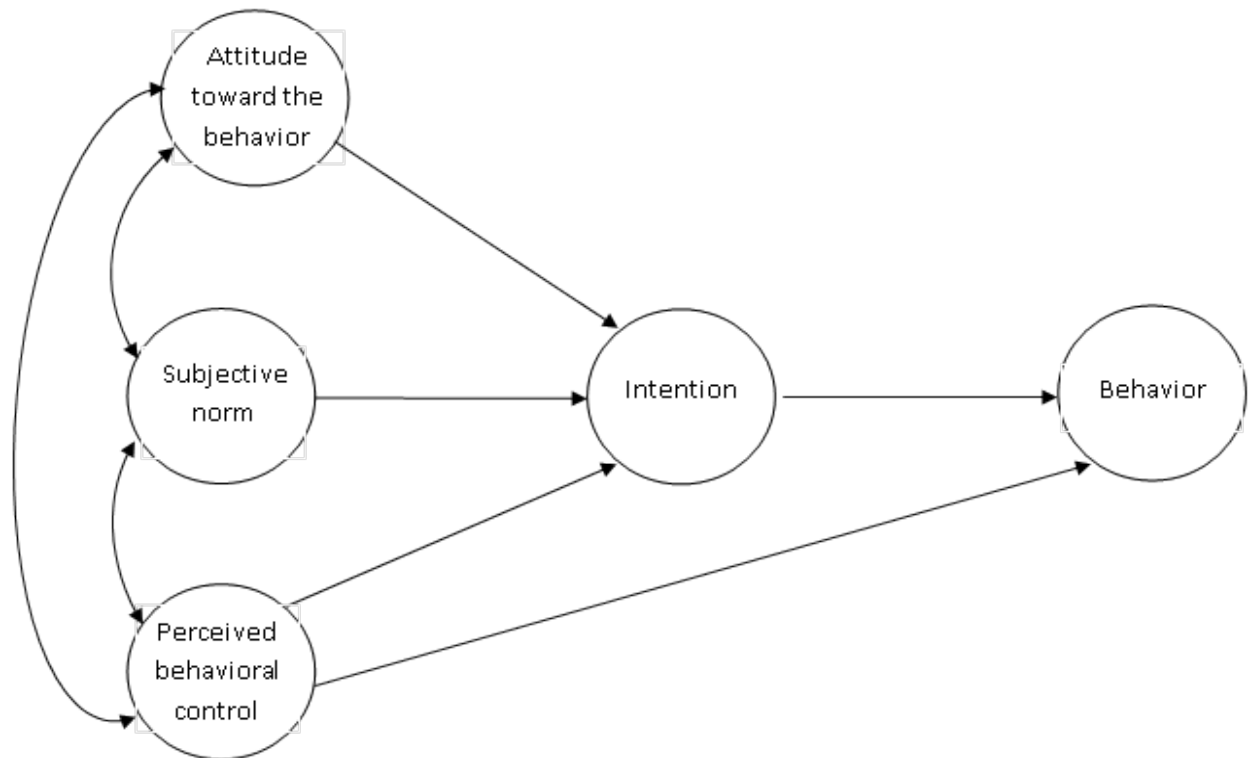
Preexisting and deeply rooted misperceptions about the health risks of ST products relative to cigarettes may mediate the impact of a single exposure to the proposed claim on attitudes toward a perceived health benefit of switching from cigarette smoking to the candidate product. Adding further complexity, a cigarette smoker's attitude toward a modified risk message may be influenced by believability of the claim itself due to public opinion about the tobacco industry and decades of public health messaging against tobacco products and ST

products in particular (Fix et al., 2017). These findings, that believability influences the impact of a tobacco product risk claim, are consistent with the principles outlined in the TPB.

Overall, a cigarette smoker will internally process the modified risk message through the cognitive schema developed over his/her lifetime exposure to different public health messages regarding ST products and mistrust of industry. This will inform their willingness to change their attitudes and beliefs enough to manifest into behavioral intentions to use the candidate product. It is also worth noting that a variety of other factors (e.g. presence of smokers around them) could reportedly influence a cigarette smoker's readiness to change their tobacco use (Buczkowski, Marcinowicz, Czachowski, & Piszczek, 2014; Lee & Kahende, 2007; Smith, Carter, Chapman, Dunlop, & Freeman, 2015). Taken together, it is not surprising that we did not observe immediate changes in behavioral intentions to try or use the candidate product, based on a single exposure to the proposed claim. We contend that long-term dedicated efforts that responsibly deliver the proposed modified risk message will be necessary to change tobacco consumers' attitudes, subjective norms, and perceived behavioral controls. Consistent and accurate messaging from all key stakeholders (e.g., the tobacco industry, public health, and regulatory agencies) will be needed to maximize the likelihood of an attitude change toward ST products and, ultimately, complete switching to the candidate product.

6.3.3.4.   Summary

We believe that switching to the candidate product will most likely be observed among ATC who already use MST (either exclusive use or dual use), or among AS who are open to alternate tobacco product use. The results of our CCI Study indicate that current MST users or dual users were generally more receptive to the idea of candidate product use compared to smokers (based on higher pre-test scores). Even among these groups, however, initial interest using a single exposure to the claim is low.

We expect low likelihood of initiation of regular ST use among current smokers in terms of either switching to the candidate product or dual use. We believe that the misperceptions of harm from MST use (Section 6.2) could be a substantial barrier to entry into the MST category for ATC and may contribute heavily to the relatively low proportion of ATC indicating their intent to use the candidate product. Additionally, the single exposure to the proposed claim language may not have provided a sufficiently compelling motivation for participants to signal an intention to try, use, or switch to the candidate product. As described in the TBP model, several factors can influence attitudes, intentions, and behavior.

Although results of our CCI Study suggest minimal increase in likelihood of use of the candidate product after a single exposure to the proposed modified risk claim, we anticipate that repeated and consistent messaging that can affect attitudes and subjective norms will encourage adult smokers (exclusive and dual users) to start using the candidate product. To provide the agency with additional information on the likelihood of use, we propose a postmarket surveillance program (Section 8.1) to monitor actual use behavior relative to the candidate product under real world conditions.

6.3.4.   The Likelihood That Tobacco Users Will Switch to or Switch Back to Other Tobacco Products with Higher Levels of Risk

A number of factors influence product choices, making a premarket assessment of the likelihood of adopting the candidate product and switching to another more risky tobacco product problematic. Direct or conclusive evidence of this behavior (sometimes referred to as "gateway") will become available once the candidate product is marketed with the proposed claim, following FDA authorization; such behavior will be monitored during postmarket surveillance (Section 8.1). Under premarket conditions, our CCI Study indicates that tobacco users have limited interest in adopting the candidate product after reviewing the modified risk claim. Therefore, if tobacco users do not adopt the candidate product, then the question of switching back to cigarettes remains a very low probability proposition.

Substantial scientific evidence from published literature shows that smoking cigarettes is the most predominant and most harmful form of tobacco product use. Accordingly, we will focus our discussion here on the potential for adoption of the candidate product (likely by cigarette smokers or dual users) and, subsequently, movement back to cigarettes. While the term gateway is more commonly associated with non-tobacco users who adopt ST and subsequently progress to cigarette smoking, it could also apply to situations where smokers adopt ST and then subsequently revert back to smoking. Current available evidence is inadequate to infer either the presence or absence of a causal relationship between ST use and subsequent smoking.

After analysis of 1998 National Health Interview Survey tobacco use history data for 13,865 males aged 18 years or older, Tomar (2002) found a higher cigarette smoking prevalence among former (39.4%) and some-day (38.9%) ST users than among daily ST users (19.2%) or never users (25.4%). In addition, former ST users who currently smoked cigarettes comprised 2.5% of the study population, former cigarette smokers who currently used ST represented 0.9%, and dual users accounted for 1.1%. These results suggest that ST users are more likely to switch to smoking than vice versa; however, this cross-sectional survey did not ask about age of first ST product use, a key factor in understanding gateway behaviors.

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 and 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 a lower probability of transitioning to cigarettes 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.

Tomar reports that ST may act as a starter product for, or gateway to, smoking based on the CDC Teenage Attitudes and Practices Survey (TAPS). This analysis, however, did not take into account well-established psychosocial predictors of smoking initiation. When O'Connor

et al. (2003) considered psychosocial factors using a multivariate model; these effects were no longer significant. The authors state that, "Tomar's analysis should not be used as reliable evidence that smokeless tobacco may be a starter product for cigarettes."

Studies by Haddock et al. (2001), Tomar (2003), and Severson et al. (2007) have all found that both past and current users of ST were more likely than never-ST users to become smokers. In contrast, Kozlowski et al. (2003) reanalyzed some of the data used in these studies and concluded that ST use could not logically cause smoking. Timberlake et al. (2009) used a propensity scoring method that controlled for the probability of an event being conditional on a series of predictor variables as a way of reducing the diversity of background characteristics and overlapping confounding factors. The authors concluded "…smokeless tobacco use appears not to be an important predictor of smoking initiation…."

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, Levy, and Meza (2017) analyzed ST use and cigarette smoking transitions using the TUS-CPS (2010 to 2011). In their study, the proportion of males who switched from ST to cigarettes (1.4%) was comparable to the proportion who switched from cigarettes to ST (1.2%). This suggests that transitions between ST use and cigarette smoking may be bi-directional.

The published literature clearly establishes that people consume tobacco products for many reasons. Recent studies on smokers' decision-making suggest that it is "not the mere inclination to take risk that drives smokers' behavior…but rather their inclinations not to engage in choices that are inconvenient…and to be more easily tempted by the typical pleasurable alternative" (Zhu et al., 2009). Compared with never-users of tobacco, ST use could be associated with an increased probability of cigarette smoking; ST use, however, does not appear to cause cigarette smoking. Rather, it is one of several risky behaviors associated with cigarette smoking among predisposed individuals.

Overall, the available evidence is mixed. Tobacco product category switching behavior in exclusive ATC appears to be rather infrequent, but when switching does occur, it is more likely to be from ST or dual use to cigarettes (Zhu et al., 2009), and a proportion of ST users may switch to cigarettes when they cannot or do not want to use ST (Chakravorty & Chakravorty, 1997). Effective communication of the accurate risk differential between ST and cigarettes might prevent ST users from reverting back to smoking. Smokers who use ST as a quit method may have a lower smoking relapse rate than those who use other quit methods (Rodu & Phillips, 2008). The evidence from current literature, therefore, is inadequate to infer the presence or absence of a causal relationship between ST use and subsequent cigarette use in current tobacco users.

6.3.4.1.   Summary

Some investigators maintain that the use of ST "may be a gateway form of nicotine dosing…that may lead to subsequent smoking" (Henley et al., 2007). Together, many

behavioral and social issues fuel the ongoing debate about the use of ST as a possible gateway to cigarette smoking (Section 7.5.3-1 and Section 7.5.3-2).

It is difficult, if not impossible, to estimate, in a pre-market setting, the likelihood of transitioning from a current state of tobacco product use to a future state (i.e., adopting the candidate product) and then further transitioning to yet another future state (i.e., switching to other tobacco products that present higher risk). Nonetheless, we conclude that the evidence currently available is inadequate to infer either the presence or absence of a causal relationship between ST use and subsequent smoking.

As we discussed previously, interpreting or predicting changes in tobacco product use behavior is complex. We believe it is possible that many of these transitions could be related to a lack of adequate awareness of the risk continuum. We do not anticipate that current MST users who adopt the candidate products would switch to smoking at any accelerated rate, particularly as they become aware of the accurate risk differential between the candidate product and cigarettes. Switching between tobacco products, however, is likely for some current smokers who may transition over time to the candidate product. To provide the agency with additional information on the likelihood of use, we will track actual use behavior of adult tobacco consumers using the candidate product under real world conditions during postmarket surveillance (Section 8.1).

6.3.5.   The Likelihood of Dual Use with Other Tobacco Products

We do not expect to see complete and immediate transition from cigarettes to the candidate product for the majority of AS. Some period of multiple tobacco product use is likely, even among AS who are committed to transitioning to exclusive use of the candidate product. Currently, however, we are not aware of any reliable means of accurately predicting the duration of this dual use state for a typical smoker. Ultimately, a smoker's beliefs and motivations will determine the success and duration of this transition. The emphasis on "switching completely" in the proposed modified risk claim is intended to minimize dual use and encourage exclusive use among AS. The term *dual use* has been used to describe the concurrent use of multiple tobacco products (primarily ST and cigarettes).[8] Dual use, however, broadly refers to AS who occasionally use MST and MST users who occasionally smoke. Exclusive cigarette smoking is a significantly more prevalent behavior than dual use

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[8] Dual use could apply to any other non-cigarette tobacco product (e.g., cigars, hookahs, etc.), but the information related to these consumers is relatively sparse. The term *dual use* is not intended to mean those who concomitantly use ST while smoking, but rather describes situations where products are alternated at various times for a variety of reasons. In some instances, the term *polytobacco use* appears in the scientific literature. Our review of the literature indicates some inconsistency in defining a smoker, a former smoker, or dual use. Additionally, the nuances of alternating product usage are not well defined or captured. In some instances, cigarette smokers use MST on occasion, while in other cases MST users smoke an occasional cigarette. A few consumers report daily use of both products, while others report less frequent (weekly or monthly) occurrence. Some consumers, especially adolescents, are likely experimenting with multiple tobacco products and have not reached a steady state of tobacco use. Others may be using alternative tobacco products to stop smoking.

of ST and cigarettes.[9] Whereas exclusive cigarette smoking has declined since the early 2000s, dual use prevalence has remained relatively stable. During 2013-2014, the CDC estimated that 21.3% of adults used some form of tobacco, with about 17% using cigarettes and 2.5% using smokeless tobacco.[10] In the 2012 National Survey on Drug Use and Health, the CDC estimated that 1.1% of youth (aged 12-17), 3.9% of young adults (aged 18-25), and 1.2 % of adults (aged 26 or older) used ST and at least one other tobacco product.[11]

In Section 3.2.3 we report prevalence of concurrent use of MST and other tobacco products. Based on our analysis of 2014 NSDUH data, 1% of the entire U.S. adult population report past 30-day use of both MST and cigarettes. Some data suggests that Copenhagen® Snuff Fine Cut users are less likely to be dual users. Our analyses of PATH data show that 40% of total adult MST consumers report past 30-day use of cigarettes; whereas, 20% of Copenhagen® Snuff Fine Cut consumers report past 30-day use of cigarettes (Section 3.2; Table 3.2-6). In our Tracking Study (Section 3.2), 30% of total adult MST consumers report past 30-day use of cigarettes, whereas 19% of Copenhagen® Fine Cut consumers report past 30-day cigarette smoking (Section 3.2; Table 3.2-6).

In a study of ST users who were seeking treatment with a transdermal nicotine system (dual users excluded from enrollment), Hatsukami et al. (1999) found that among ST users who had ever smoked cigarettes (69.2%), approximately 24.5% indicated smoking currently, with the majority smoking less than one cigarette per day (83.8%).

For some tobacco product users, adoption of the candidate product may mean continued tobacco product use, although with less risk. Kasza et al. reported that among a sample of AS, 53% of ST users reported using ST to cut down on the amount of cigarettes smoked, and 43% reported ST use to help with quitting cigarettes (Kasza et al., 2014). Frost-Pineda et al. reviewed the available literature on health effects and trajectories of use among dual users from a variety of U.S. and European epidemiological studies (Frost-Pineda, Appleton, Fisher, Fox, & Gaworski, 2010). On the basis of the collective trajectory data from independent studies conducted in the U.S. and Sweden (Tillgren, Haglund, Lundberg, & Romelsjo, 1996; Wetter et al., 2002; Zhu et al., 2009), the authors noted that the data "…suggest that, while over time, dual users are less likely to stop all tobacco use altogether, they are more likely to reduce smoking intensity (i.e., transition away from cigarettes)" (Frost-Pineda et al., 2010).

As reported in Section 3.2.2 (Table 3.2-3), adult MST consumers, who report using cigarettes in the past 30 days, report smoking on an average of 24 to 26 of the past 30 days. Participants

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[9] As mentioned in Section 3.2.3, the proportion of MST consumers reporting dual use with cigarettes ranged from approximately 30% to 40% depending on the survey

[10] http://www.cdc.gov/tobacco/data_statistics/mmwrs/byyear/2016/mm6527a1/intro.htm Tobacco Product Use Among Adults—United States, 2013–2014 (accessed 2016 Jul 18).

[11] http://www.cdc.gov/tobacco/data_statistics/fact_sheets/smokeless/use_us/index.htm 2012 National Survey on Drug Use and Health, U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General(http://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/index htm). Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014 (accessed 2016 Jul 18).

report smoking an average of 13 to 16 cigarettes on days they smoked. The NSDUH data shows a lower pattern: dual users report smoking on an average of 19 days in a month and smoking nine cigarettes on days they smoked. Our assessment of cigarette use among MST users, as described in Section 3.2.3, suggests that Copenhagen® Snuff Fine Cut and MST consumers who report using the fine cut form smoke fewer cigarettes per day than MST users overall (Table 3.2-7), but the data should be interpreted with caution due to the small sample sizes.

Observations from Norway may provide some insight regarding transition from dual use to exclusive ST use, albeit with some limitations regarding direct application to the U.S. consumer. In Norway, many dual users expressed an interest in switching to exclusive snus use. Lund et al. (2013) reported no significant difference between dual users (49.8%; 95% CI, 43.5–56.1; n = 238) and exclusive smokers (43.2%; 95% CI, 39.5–46.9; n = 679) with respect to the proportion that planned to quit smoking within the next six months. However, a significantly higher proportion of dual users (74.4%; 95% CI, 68.8–80.0; n = 235) than exclusive smokers (61.3%; 95% CI, 57.6–65.0; n = 658) reported that they most definitely or probably would be totally smoke-free five years into the future. The patterns of tobacco product use behavior in Norwegian males suggest that, over time, the prevalence of dual use has declined and exclusive use has increased, although not proportionately. The share of Norwegian men who reported daily or occasional use of cigarettes, but no other tobacco product, declined from close to 50% in 1985 to below 20% in 2010. For the same period, the percent of exclusive snus users (daily or occasional) increased from 3% to 12%. The segment of dual users of cigarettes and snus has been stable (4%–7%) for the whole period. The overall percentage of tobacco users decreased from 54.4% to 37%. While these relationships reflect only an association, these data suggest that dual use is not a fixed state, but rather part of a transition period away from dual use.

As indicated by the transition rates summarized from (Tam, Day, Rostron, & Apelberg, 2015) in Section 7.4.2.2.2, a person who adopts a dual-use state increases the probability of transitioning to the exclusive MST use state (i.e., lower relative risk state), as compared with the probability of an exclusive smoker directly transitioning to exclusive MST use. For example, the 4 year adult transition rate from dual use to exclusive MST use is 17.4 percent, as opposed to the 4 year adult transition rate from exclusive smoking to exclusive MST use, which is 1.4 percent.

We asked participants in our CCI Study (Section 7.3.2) if they were likely to use the candidate product in addition to cigarettes, before and after seeing the modified risk claim. After adjusting for covariates, there were no statistically significant differences in intentions to dual use between the Test and Control conditions in any subgroup (Table 6.3-3). Similar findings resulted when the data were analyzed on the basis of special subgroups including Low Health Literacy, Normal Health Literacy, or age (legal age to purchase tobacco up to age 24) (sub-group data not shown). We believe, however, that since dual users have already made the choice to use ST products, they would likely be more receptive than other tobacco users to a modified risk claim and switch completely to the candidate product.

Table 6.3-3: **Composite Scores (Unadjusted Means) of Responses to a Question About the Likelihood of Dual Use of Candidate Product and Cigarettes Among Current Tobacco Users.**

Group	Condition	Intention to Dual Use[1]	
		Pre	Post
ASPQ	Control (n =401)	2.19	2.06
	Test (n = 406)	2.15	2.05
ASNPQ	Control (n= 403)	2.33	2.22
	Test (n = 398)	2.24	2.23
Dual Users	Control (n = 418)	4.19	3.97
	Test (n = 422)	4.32	4.15

Source: Appendix 7.3.2-1; Table 25
ASPQ = Adult Smokers Planning to Quit, ASNPQ = Adult Smokers Not Planning to Quit
[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 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: I plan to use Copenhagen® Snuff in addition to regular cigarettes Group sizes ranged from 398 to 422.

6.3.5.1.   Summary

Studies in the literature show that consumers who use multiple tobacco products do so for various reasons. Some current cigarette smokers who wish to continue the use of tobacco products are initiating ST use as an approach to smoking cessation, since ST may provide a suitable substitution for smoking.

As consumers transition from the use of one tobacco product to another, some level of dual use is expected, despite our emphasis on complete switching in the proposed modified risk claim. It is unlikely that cigarette smokers will immediately adopt the candidate product, particularly given the deep-rooted beliefs that ST is as harmful or more harmful than, cigarettes. Currently, however, we cannot establish the duration of the transition period for the candidate product. Ultimately, an individual's beliefs and motivations will guide the success and length of a transition from more risky products to lower risk products. Considering the fewer serious health risks associated with ST use as compared with cigarette smoking (Section 6.1), providing dual users with truthful and accurate information about the candidate product authorized by FDA could facilitate this transition and provide a public health benefit. Our proposed postmarket surveillance (Section 8.1) plan will provide the agency with additional information related to dual use of the candidate product with other tobacco products.

6.3.6. The Likelihood That Users Who May Have Otherwise Quit Using Tobacco Products Will Instead Use the Product

We are not aware of a validated approach that accurately quantifies the possible interception of tobacco quitters by the candidate product if marketed with the proposed modified risk claim. No single study prospectively and specifically examines the likelihood that consumers who may have otherwise quit using tobacco products (in this case, "imminent quitters" of cigarettes) will instead use ST. The published literature supports that some AS use ST to cut down on smoking, as an alternative to quitting tobacco products altogether, or to help quit smoking (Section 7.5.2-1 and 7.5.2-2). Due to the cross-sectional nature of several of the studies and attrition of study participants or short follow-up periods in the longitudinal studies, reliable long-term, within-subject trajectories of tobacco product use are generally unavailable and the current literature does not provide conclusive evidence to determine if ST use in the absence of a modified risk tobacco claim either promotes or hinders cessation of smoking in the U.S.

Results of our CCI Study (Section 7.3.2) do not indicate that the proposed claim for the candidate product is likely to alter current smoking or tobacco product cessation intentions substantially. Table 6.3-4 shows the responses of adult tobacco user sub-groups in the CCI Study when asked about intentions to alter tobacco product use. Both Test and Control groups reported a reduction in intent to quit smoking after viewing the advertisement materials (either with or without the modified risk claim), which was not statistically significant. The reason for this observation may not be readily apparent; this phenomenon, however, may result from a potential "ceiling effect," which could be an artifact of the selection criteria. In this case, the question "Are you planning to quit in the next 30 days," posed at screening, to define the ASPQ subpopulation. Thus, by default, all ASPQ received a premeasure of 100% for intention to quit, and exposure to stimuli in either condition (Test or Control) could only result in the same or reduced intent to quit. Similar levels of reduction in intent to quit in both groups (Test and Control) suggest that this outcome measure is prone to variability. This observation has been corroborated in literature where intent to quit measures have been reported to be variable and should be interpreted with caution (Bondy et al., 2010; Peters & Hughes, 2009). Nevertheless, lack of statistical differences between the Test and Control groups in the CCI Study on intent to quit measures suggests that the proposed claim is not likely to alter the quitting trajectory of adult smokers who intend to quit smoking.

Table 6.3-4: Intention of Current Tobacco Users to Stop Smoking Cigarettes, or Quit Tobacco Product Use Altogether

Group	Intention[1]	Percent responding yes			
		Control		Test	
		Pre	Post	Pre	Post
ASPQ	Stop smoking	100	86[a]	100	86
	Quit all tobacco products	87	77	89	78

Group	Intention[1]	Percent responding yes			
		Control		Test	
		Pre	Post	Pre	Post
ASNPQ	Stop smoking	0	9	0	4
	Quit all tobacco products	1	8	2	5
MST Users	Stop smoking	NA	NA	NA	NA
	Quit all tobacco products	4	11	7	11
Dual Users	Stop smoking	11	21	16	23
	Quit all tobacco products	8	16	10	13

Source: Stop smoking – Appendix 7.3.2-1; Table 35, Quit tobacco – Appendix 7.3.2-1; Table 40
ASPQ = Adult Smokers Planning to Quit, ASNPQ = Adult Smokers Not Planning to Quit
[1] Intention was assessed before (pre) or after (post) reading an advertisement containing the proposed claim language (Test) or reading an advertisement without the proposed claim language (Control). Values represent the percent of positive responses to the questions: Stop Smoking - Are you planning to quit smoking cigarettes in the next 30 days? Yes / No; Quit tobacco - Are you planning to quit the use of all tobacco products in the next 30 days? Yes / No. NA = Not assessed. Group sizes ranged from 398 to 439.

The ASNPQ group showed a statistically significant difference between the Test and Control conditions for intentions to quit smoking based on a simple t-test (p = 0.008, Appendix 7.3.2-1; Table 66). While both Test and Control conditions showed a nominal increase in intention to quit smoking post-exposure, the magnitude of change was larger for the Control Condition (M = 0.09) than the Test Condition (M = 0.04). The magnitude of this difference was relatively small and not statistically significantly different based on the Logistic Regression Model (Appendix 7.3.2-1; Table 37), which, unlike the unadjusted comparison based on a t-test, takes into consideration the effects of covariates.

After adjusting for covariates, we observed no statistically significant differences between the Test and Control conditions among current MST users (either exclusive or dual users) or AS. Similar findings resulted when the data were analyzed on the basis of special subgroups, including Low Health Literacy, Normal Health Literacy, or age (legal age to purchase tobacco up to 24) (data not shown).

Results of our CCI Study (Section 7.3.2) also confirmed that former tobacco users were not persuaded to reinitiate tobacco use after seeing the candidate product and proposed modified risk claim (Table 6.3-5). Statistical analysis (ANCOVA) indicated no significant differences between changes in Test and Control responses.

Table 6.3-5: Composite Scores of Responses to Statements or Questions Related to Trial or Use of the Candidate Product Among Former Tobacco Users

Condition	Intention to Try[1]		Intention to Use[1]	
	Pre	Post	Pre	Post
Control (n = 400)	1.33	1.29	1.30	1.25
Test (n = 402)	1.38	1.33	1.30	1.27

Source: Stop smoking – Appendix 7.3.2-1; Table 7, Quit tobacco – Appendix 7.3.2-1; Table 16

[1] Values represent the average score of responses to statements or questions rel2ted to trial or use of the candidate product before (pre) or after (post) reading an advertisement containing the proposed claim language (Test) or reading an 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.

6.3.6.1.   Summary

Harm reduction will be realized if ATC (particularly those unable or unwilling to stop using tobacco) switch to the candidate product and in the process stop smoking. Although some smokers report using ST as an approach to altering smoking behaviors and achieving smoking cessation, it may lead to continued tobacco use (in the form of ST). As noted by Frost-Pineda (2010), however, "The fact that a greater proportion of smokers who switch to smokeless tobacco continue to use tobacco products (primarily in the form of smokeless tobacco) compared with smokers who do not is greatly mitigated by the substantial risk differential between the two product categories…"

Our consumer study assessing the possible impact on cessation intentions of marketing the candidate product with the proposed claim indicated little reason to believe that smoking cessation trends would be adversely impacted. We will continue to monitor in postmarket surveillance (Section 8.1) the likelihood of changes in tobacco use behavior in current and former tobacco product users under real-world conditions, once the proposed modified risk claim is authorized by FDA. The current scientific evidence does not lead us to conclude that marketing the candidate product with the proposed claim would hinder smokers' attempts to quit smoking. Rather, we anticipate that such a message would accelerate smoking cessation.

6.3.7.   The Likelihood That Users Will Use the Product as Intended or Designed

The candidate product is an established MST product that has been marketed for nearly two centuries.[12] Tobacco consumers understand that MST products are designed for oral consumption and use the product by taking a pinch and placing it between the lower lip and gum. USSTC and other manufacturers of such tobacco products do not issue specific instructions for use; rather consumers have self-determined level and frequency of use. We include additional description regarding the use behavior of the candidate product in Section 3.2.1. The long history of MST use does not lead us to conclude that future tobacco consumers (including those only familiar with cigarettes), with the addition of the proposed modified risk claim, will use the candidate product any differently from other MST products.

6.3.8.   Abuse Potential

FDA recommends in Section VI (A)(2) of the 2012 Draft MRTPA Guidance that applicants submit nonclinical, and/or human studies, to assess the abuse potential of the product as compared to other tobacco products on the market as part of the application. These recommendations fall outside the scope of the Tobacco Control Act (TCA) as Congress showed no intent to require such information in MRTPAs. In Section 911, Congress provided specific categories of testing and data for applicants to submit in MRTPAs. Notably, data gathered from testing of abuse liability is not included in Section 911 submission requirements, nor is the term "abuse liability" found anywhere within the text of the TCA.

Our approach[13] to addressing abuse potential focuses on the rate and extent of nicotine delivery and any resulting behavioral effects. We base our assessment for the candidate product on three sources of evidence:

- a clinical study evaluating the pharmacokinetics, subjective effects, and *ad libitum* product use behavior of the candidate product relative to cigarettes and nicotine polacrilex gum (Appendix 7.3.1-1);

- a review of the literature on the abuse and dependence potential of U.S MST products, and ST products in general, relative to conventional cigarettes and NRT (Section 7.5.2-1 and 7.5.2-2); and

- published reports of misuse and abuse for the candidate product (Section 7.5.2-1 and 7.5.2-2).

On the basis of our analysis, we conclude that the abuse potential of the candidate product is lower than that for subjects' own brand cigarettes and is lower than that of the nicotine polacrilex gum. We derive our conclusions based on the rate of nicotine uptake in adult smokers who use MST, responses to subjective measures and product use behavior.

[12] The candidate product was marketed in the U.S. from 1822 through February 15, 2007.

[13] Carter et al. (2009) and Hennigfield et al. (2011) have proposed that abuse potential of novel tobacco products can be assessed by utilizing nicotine PK and subjective responses that provide insights on reinforcing effects from product use.

6.3.8.1. Clinical Investigation

We conducted an open-label, randomized, two-stage, three-way crossover study (Study #ALCS-RA-17-02-MST) designed to investigate the reinforcing effects of the candidate product by measuring rate and extent of nicotine uptake, responses to subjective questionnaires and product use behavior (Appendix 7.3.1-1). We compared the controlled use of the candidate product (2 g pinch used for 30 mins) relative to adult subjects' own brand of cigarettes and mint flavored Nicorette® polacrilex gum[14] (4 mg used for 30 mins). The study included (n=24) adult cigarette smokers (21+ years of age) who also use MST.

We conducted this study in two stages (Figure 6.3-4). During Stage 1, study participants used the study products under *ad libitum* conditions for four hours. Stage 2 involved controlled product use and measurement of nicotine plasma levels and subjective responses at periodic time intervals.

Figure 6.3-4: Overall Study Design
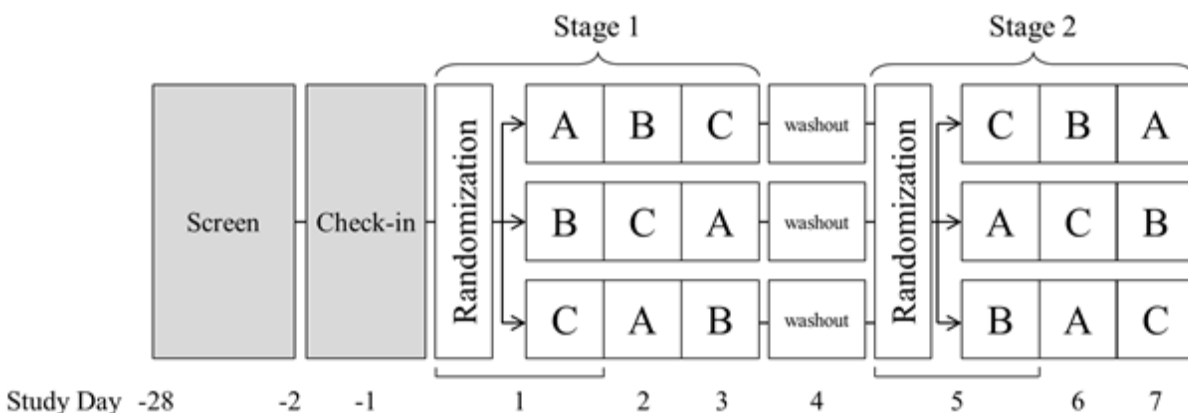
Product A: A test MST product produced to the identical specifications as for the Copenhagen® Original Fine Cut Snuff product marketed as of February 2007 (Test Product). See Appendix 7.3.1-2 for documentation related to factory batch release and Appendix 7.3.1-3 for analytical testing results for nicotine levels (12.44 mg/g tobacco) measured as is in the product).
Product B: Subject's Own Brand Cigarette (Reference Product)
Product C: Nicorette® Fresh Mint™ polacrilex gum, 4 mg (Reference Product)

[14] Hereafter referred to as "nicotine gum"

The objectives of the study were:

1. Characterize the nicotine pharmacokinetic (PK) profile of the candidate product relative to the participants' own brand of cigarettes and nicotine polacrilex gum under controlled use conditions (Appendix 7.3.1-2 and Appendix 7.3.1-3)

2. Evaluate the subjective effects of the candidate product relative to the participants' own brand of cigarettes and nicotine polacrilex gum under controlled and *ad libitum* use conditions.

3. Characterize the product use behavior of the candidate product, participants' own brand of cigarettes, and nicotine polacrilex gum under *ad libitum* use conditions.

6.3.8.1.1. Nicotine Pharmacokinetics

Figure 6.3-5 displays the mean baseline-adjusted plasma nicotine concentrations for the three products used in the study.

Figure 6.3-5: Mean Baseline Adjusted Nicotine Concentrations
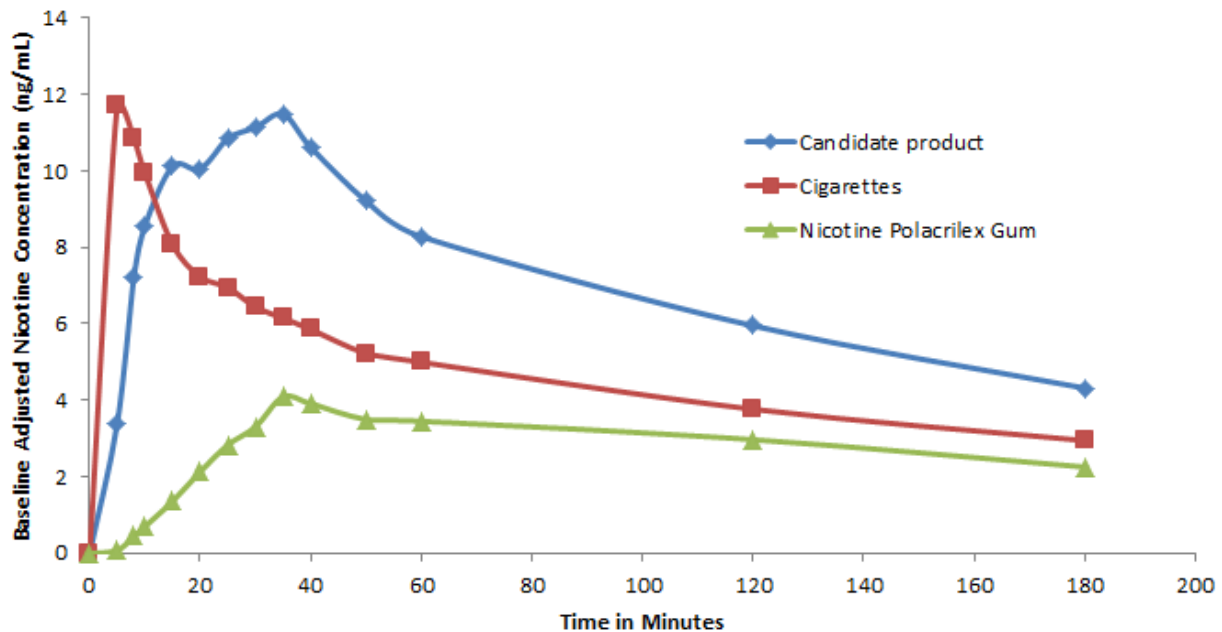
Source: Appendix 7.3.1-1; Figure 2

Program /CA212891/sas_prg/pksas/intent_adam_meangraph.sas 06SEP2017

The model adjusted geometric least square mean (LSM[15]) ratios of Cmax and AUC(0-180)[16] for the participants' own brand of cigarette were approximately 185% and 71% higher,

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[15] The Geometric Least Square Mean estimated using a linear mixed model for analysis of variance (ANOVA) on the log transformed nicotine PK parameters AUC (0-180) and Cmax. The model included sequence, study product,

respectively, than the nicotine polacrilex gum. The differences were statistically significant, confirming the sensitivity of the study design to differentiate between the reference products.

The geometric LSM ratios of Cmax for the candidate product, although not statistically different from the participants' own brand of cigarette, were approximately 12% lower. Geometric LSMs ratios of $AUC_{(0-180)}$ for the candidate product were approximately 45% higher than the participants' own brand of cigarette and the difference was statistically significant. The higher AUC results from candidate product use by participants over 30 minutes as compared to cigarettes, which are consumed in ~ 5 minutes. Additionally, participants consume a greater amount (~2 g) of the candidate product compared to a cigarette (~1 g), and a large proportion of tobacco in a cigarette is burned and lost in side-stream smoke. Similar plasma nicotine levels are noted in other reports with respect to ST products (Benowitz, Porchet, Sheiner, & Jacob III, 1988).

The geometric LSMs ratios of Cmax and AUC(0-180) for the candidate product were approximately 151% and 147% higher, respectively, than the nicotine polacrilex gum and the differences were statistically significant. The Tmax for the candidate product (~26 mins) was later than that for the own brand cigarette (~8 mins), but earlier than that for the nicotine polacrilex gum (~54 mins).

6.3.8.1.2. Subjective Effects

Subjective measures of satisfaction were assessed using the Tobacco/Nicotine Withdrawal questionnaire[17] and the Direct Effects of Product questionnaire,[18] which have been frequently used by other established researchers in this field to assess reinforcing effects (Carter et al., 2009; Cobb, Weaver, & Eissenberg, 2010; Hanson, O'Connor, & Hatsukami, 2009).

Two primary measures were derived from these instruments:

- maximum reduction in response for subjective ratings of "Urge to Smoke" ($E_{max-urge}$) relative to pre-use following the product use under controlled use condition; and

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period, and age group (equal to or below median age and above median age), as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term.

[16] PK parameters for nicotine were computed from the individual plasma concentrations applying a non-compartmental approach using appropriate validated PK software (e.g., Phoenix® WinNonlin®, Version 6.3). Cmax= Maximum measured plasma concentration over the duration of the measurement interval for the product use.; AUC(0-180) = Area under the nicotine concentration-time curve calculated using linear trapezoidal summation from time zero (defined as the start of the Product Use Episode) to 180 minutes (or the last quantifiable concentration during that interval).

[17] The Tobacco/Nicotine Withdrawal questionnaire includes questions about urges to smoke, anxiousness, difficulty concentrating, impatience, and craving a cigarette.

[18] The Direct Effect of Product Questionnaire included the following questions: 1.Is the product "Pleasant" right now?; 2. Is the product "Satisfying" right now?; 3. Is the product making you feel "Calm" right now?; 4. Is the product helping you "Concentrate" right now?; 5. Is the product making you feel more "Awake" right now?; 6. Is the product making you feel "Sick" right now?; 7. Is the product reducing your "Hunger" for food right now?'; 8.Would you like "More" of the product right now?

- maximum response ($E_{max-plst}$) for subjective ratings of "Pleasant" following the product use under controlled use condition.

As measured by the Tobacco/Nicotine Withdrawal ($E_{max-urge}$) questionnaire, "Urge to Smoke" showed no statistically significant difference between the candidate product as compared to use of the participant's own of brand cigarette (A vs B) or nicotine polacrilex gum (A vs C) (Table 6.3-6). The maximum reductions in $E_{max-urge}$ following nicotine polacrilex gum were significantly lower compared to a participant's own brand of cigarette (A vs C).

Table 6.3-6:   Statistical Comparison of Tobacco/Nicotine Withdrawal Maximum Reduction in Urge to Smoke from Pre-Use in VAS Score ($E_{max-urge}$)

Comparison	LS Means		LS Means Difference (Test - Reference)	95% Confidence Intervals	p-Value
	Test (n)	Reference (n)			
Product A vs Product B	38.51 (24)	44.67 (24)	-6.15	-20.51 - 8.20	0.3924
Product A vs Product C	38.51 (24)	29.40 (24)	9.11	-5.26 - 23.48	0.2079
Product B vs Product C	44.67 (24)	29.40 (24)	15.27	0.89 - 29.65	0.0380

Source: Appendix 7.3.1-1; Table 14
Program: /CA21981/sas_prg/pksas/pd/adam_intext_pd_statsmixed.sas 05SEP2017
n = Number of observation used in the analysis
The mixed model included product sequence, period, and product as fixed effects and subject nested within product sequence as a random effect. Cigarettes per day from the tobacco use history were used as a covariate.
Mixed model with a default (variance component) covariance structure was used.
VAS = Visual analog scale.
LS = Least-squares means: calculated from the ANOVA.
Product A = Test MST/Candidate Product (Test product)
Product B = Subject's Own Brand Cigarette (Reference Product)
Product C = Nicorette® Fresh Mint nicotine polacrilex gum (Reference Product)

In addition to the primary measure of "Urge to Smoke," the Tobacco/Nicotine Withdrawal questionnaire included questions related to anxiousness, difficulty concentrating, impatience, and cigarette cravings. Figure 6.3-6 shows the median maximum reduction in response. Overall, cigarettes consistently exhibited the maximum reduction in response to all the subjective questions, followed by the candidate product and nicotine polacrilex gum.

Figure 6.3-6: Summary of Tobacco/Nicotine Withdrawal Maximum Reduction from Pre-Use in VAS Score by Product
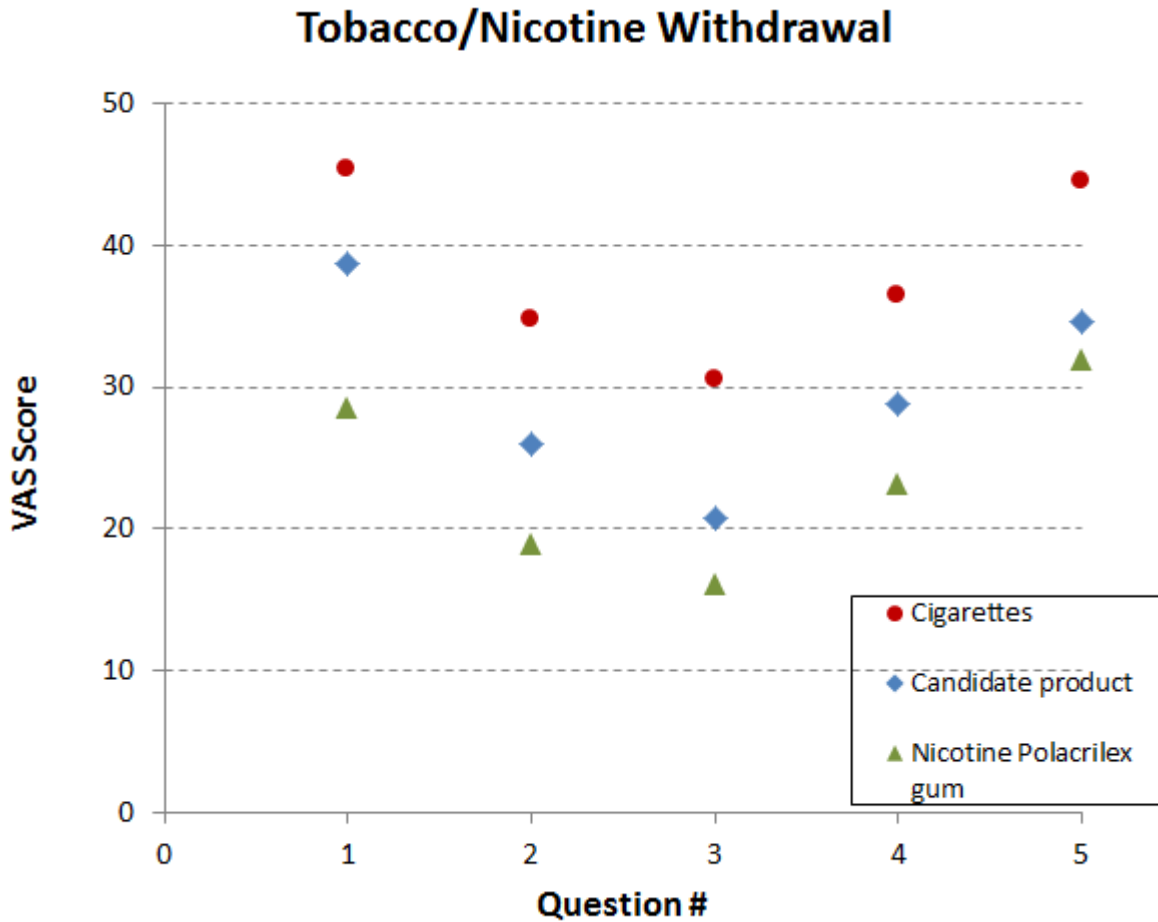
Source: Appendix 7.3.1-1; Table 13
Program: /CA21981/sas_prg/pksas/pd/adam_intext_pdparam.sas 02NOV2017
VAS = Visual analog scale; Cig = Own Brand Cigarette; Snuff = Candidate Product; Nic Gum = nicotine polacrilex gum.
The VAS anchored with "Not at All" on the left and "Extremely" on the right. Subjects place a vertical line at a place along the VAS based on how he/she feels in the moment. The study participants were asked to respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.
Question 1. Urges to smoke
Question 2. Anxious
Question 3. Difficulty Concentrating
Question 4. Impatient
Question 5. Craving a Cigarette

The maximum response to "Pleasant" on the Direct Effects of Product questionnaire ($E_{max-plst}$) following use of the candidate product and nicotine polacrilex gum (A or C vs B) were significantly lower compared to a participant's own brand of cigarette (Table 6.3-7). The primary measure of $E_{max-plst}$ showed no statistically significant difference following candidate product use as compared to nicotine polacrilex gum (A vs C).

Table 6.3-7: Statistical Comparison of Direct Effects of Product Maximum VAS Scores for Is the Product "Pleasant" Right Now ($E_{max-plst}$)

Comparison	LS Means		LS Means Difference (Test - Reference)	95% Confidence Intervals	p-Value
	Test (n)	Reference (n)			
Product A vs Product B	62.42 (24)	77.00 (24)	-14.58	-25.59 - -3.57	0.0106
Product A vs Product C	62.42 (24)	59.00 (24)	3.42	-7.59 - 14.43	0.5349
Product B vs Product C	77.00 (24)	59.00 (24)	18.00	6.99 - 29.01	0.0019

Source: Appendix 7.3.1-1; Table 16
Program: /CA21981/sas_prg/pksas/pd/adam_intext_pd_statsmixed.sas 05SEP2017
n = Number of observation used in the analysis
The mixed model included product sequence, period, and product as fixed effects and subject nested within product sequence as a random effect. We used cigarettes per day from the tobacco use history as a covariate.
Mixed model with a default (variance component) covariance structure was used.
VAS = Visual analog scale
LS = Least-squares means: calculated from the ANOVA.
Product A = Test MST Product (Test product)
Product B = Subject's Own Brand Cigarette (Reference Product)
Product C = Nicorette® Fresh Mint nicotine polacrilex gum (Reference Product)

The Direct Effects of Product Questionnaire included other questions in addition to "Is the product pleasant right now?" Figure 6.3-7 shows the maximum response to the Direct Effects of Product questions. The responses related to cigarettes measured consistently higher, followed by the candidate product and nicotine polacrilex gum.

Figure 6.3-7: Summary of Direct Effects of Product Maximum VAS Scores by Product
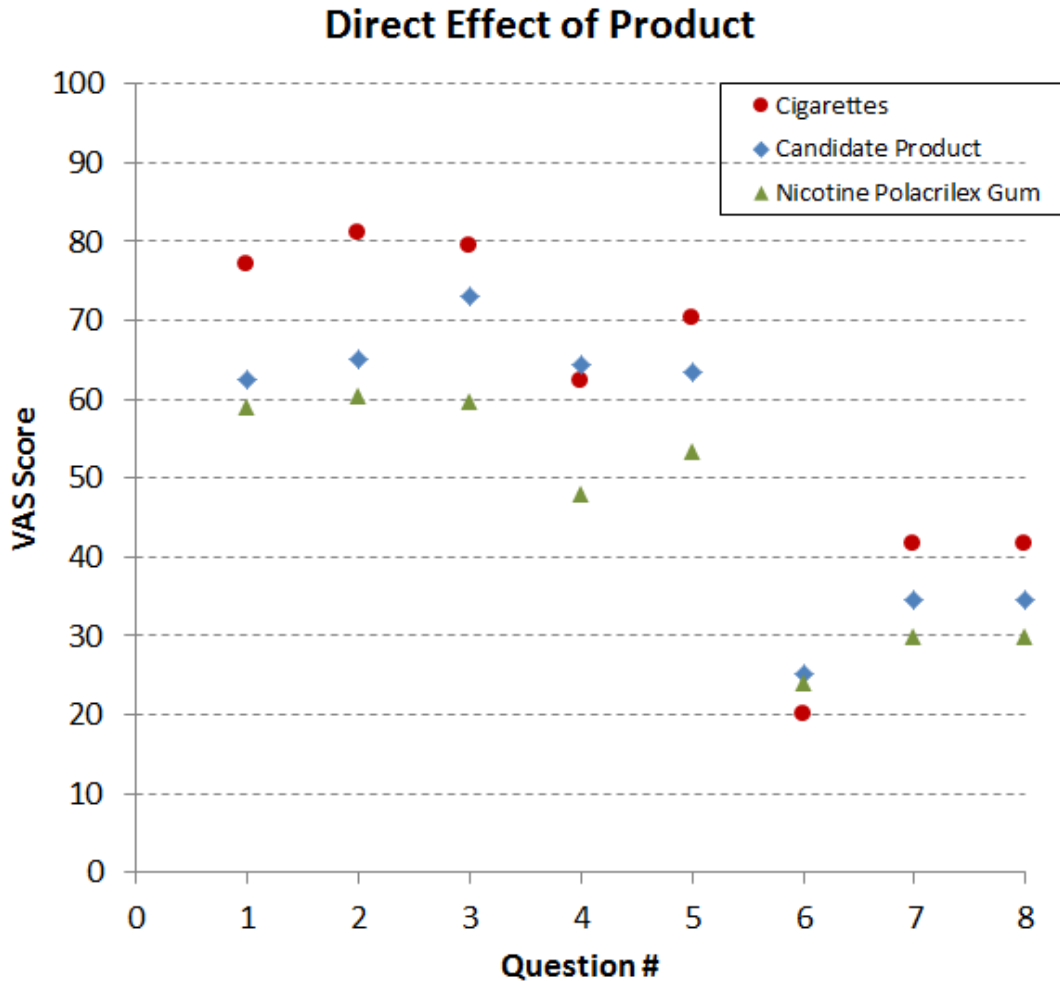
Source: Appendix 7.3.1-1; Table 15
Program: /CA21981/sas_prg/pksas/pd/adam_intext_pdparam.sas 02NOV2017
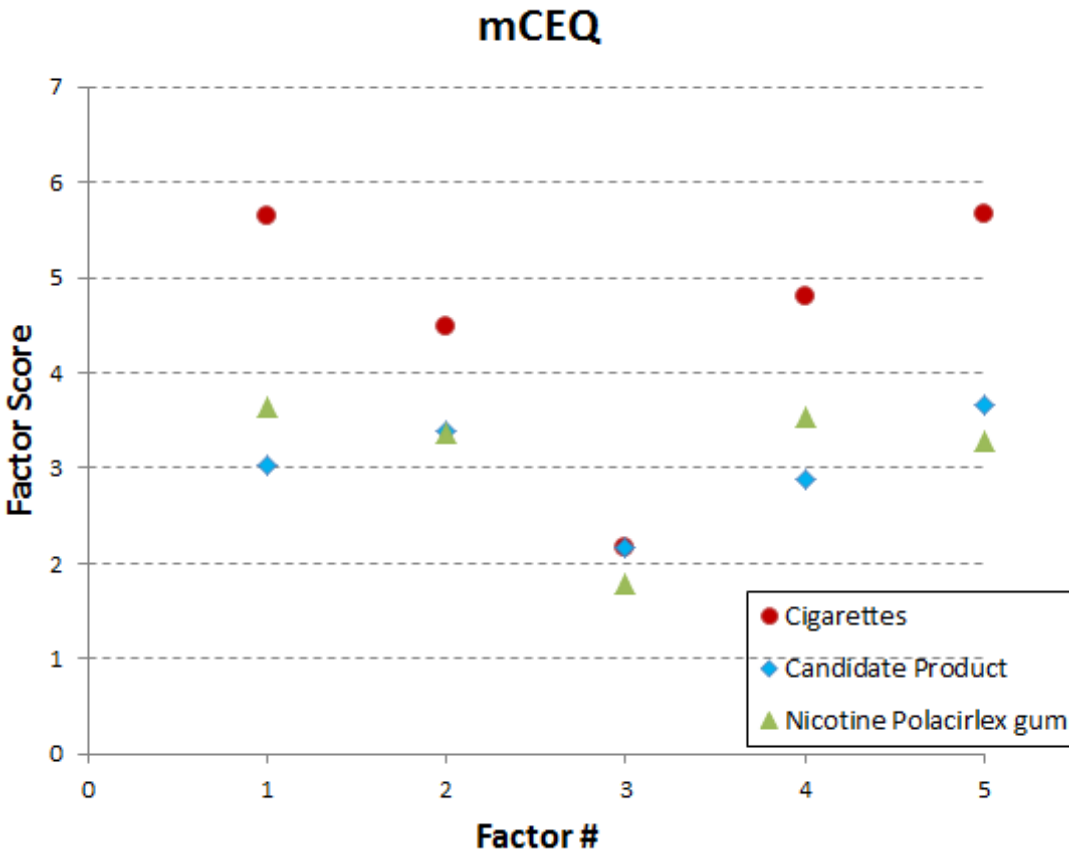VAS = Visual analog scale, Cig = Own Brand Cigarette; Snuff = Candidate Product; Nic Gum = Nicotine Polacrilex Gum.
The VAS anchored with "Not at All" on the left and "Extremely" on the right. Subjects place a vertical line at a place along the VAS based on how he/she feels in the moment. The study participants were asked to respond to each phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.
Question 1. Is the product "Pleasant" right now
Question 2. Is the product "Satisfying" right now
Question 3. Is the product making you feel "Calm" right now
Question 4. Is the product helping you "Concentrate" right now
Question 5. Is the product making you feel more "Awake" right now
Question 6. Is the product making you feel "Sick" right now?
Question 7. Is the product reducing your "Hunger" for food right now?
Question 8. Would you like "More" of the product right now?

We also measured other subjective responses under *ad libitum use* (Stage 1: Figure 6.3-4). We adapted the modified Cigarette Evaluation Questionnaire (mCEQ) for the candidate product and nicotine polacrilex gum and analyzed based on the Factors[19] as proposed by Cappelleri et al. (2007). The median scores as shown in Figure 6.3-8 below illustrate that after four hours of *ad libitum* use the study participants generally rate cigarettes higher than the candidate products and nicotine polacrilex gum for all five factors.

Figure 6.3-8: Summary of mCEQ Scores Following Use of the Test Products

Source: Appendix 7.3.1-1; Table 21
Program: /CA21981/sas_prg/pksas/pd/adam_intext_pdparam2.sas 02NOV2017 15:05
VAS = Visual analog scale, Cig = Own Brand Cigarette; Snuff = Candidate Product; Nic Gum = Nicotine Polacrilex Gum.
The mCEQ questionnaire (Detailed Questionnaire located in Appendix 7.3.1-1 [Appendix 2]), was further modified for the product being evaluated. Each of the product specific mCEQ questionnaire was based on a seven-point scale with the subjects having to mark a number that best represents how using the product made you feel (1- not at all, 2- very little, 3-a little, 4- moderately, 5-a lot, 6-quite a lot, 7 extremely). The Factor Scores were derived based on average composite scores from groups of questions from the mCEQ questionnaire.

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[19] We estimated the factors based on the average of the response scores as related to Smoking satisfaction: 1, 2, and 12 (Factor 1); Psychological reward: 4 to 8 (Factor 2); Aversion: 9 and 10 (Factor 3); Enjoyment of the sensory sensation: 3 (Factor 4) and Craving reduction: 11 (Factor 5).

Factor 1 = Smoking satisfaction (Questions 1,2 and 12)
Factor 2 = Psychological reward (Questions 4-8)
Factor 3 = Aversion (Question 9 and 10)
Factor 4 = Enjoyment of sensation (Question 3)
Factor 5 = Craving reduction (Question 11)

6.3.8.1.3. Product Use Behavior

During the *ad libitum* product use period, participants used a median of approximately two pinches, with each pinch comprising ~2g of the candidate product per pinch over the four-hour period, and the average use time was ~37 minutes per pinch. During the *ad libitum* product use period, when asked whether they would use the product again, most of the study participants selected cigarettes more often than the candidate product (Table 6.3-8). After four hours of use, the average scores were similar between the candidate product and nicotine polacrilex gum, although a slightly higher proportion indicated that they were more likely to use the nicotine polacrilex gum (n=15, 63%) than the candidate product (n=10, 42%).

Table 6.3-8:   Summary of Response to Use Product Again Overall VAS Scores (Excluding Response = 0) (Stage 1)

Product	Parameter	-50 to < 0 (n)	> 0 to 50 (n)
A	E240	-35.33 (12)	26.30 (10)
B	E240	-9.00 (1)	37.90 (20)
C	E240	-33.75 (8)	27.00 (15)

Source: Appendix 7.3.1-1; Table 18
Program: /CA21981/sas_prg/pksas/pd/adam_intext_pd_count.sas 06SEP2017
n = Number of observation used in the analysis
Product A = Test MST Product (Test product)
Product B = Subject's Own Brand Cigarette (Reference Product)
Product C = Nicorette® Fresh Mint nicotine polacrilex gum (Reference Product)
E240 = VAS score recorded after 4 hours (240 minutes) of ad libitum use
The study participants were asked to respond to the following statement based on their experience with the product used: " If given the opportunity, I would want to use this product again." Responses to Use the Product Again questionnaire recorded as VAS scores were treated as bipolar categorical variables (-50 ["Definitely Would Not"] to < 0, 0 ["Don't Care"], > 0 to 50 ["Definitely Would"]) and calculated by subtracting 50 from the original VAS score (a 0 – 100 VAS scale).

6.3.8.1.4. Summary

Based on the pharmacokinetic profile of the candidate product and subjective effects measured in our study, the abuse potential of the candidate product appears to be greater than, or similar to, that of nicotine replacement therapy (NRT) gum, but less than that of cigarette smoking.

6.3.8.2.   Literature Summary on Abuse Potential of ST Products

In the following sections, we briefly summarize literature results regarding ST abuse potential and discuss specific outcomes from pharmacokinetic studies and product effect

studies related to MST products. Appendix 7.3.1-1 presents an expanded discussion of this topic, and we summarize here the literature-based evidence as follows:

- The limited number of reports in the literature supports that misuse and abuse of ST tobacco products is rare.

- Controlled clinical trials show notable differences in subjective effects (e.g., satisfaction, liking, and craving) between ST and cigarettes, supporting that ST has relatively lower abuse potential than cigarettes.

- Overall, tobacco product use cessation rates appear to be higher in ST users than in cigarette smokers, suggesting a lower dependence potential. Fagerström and Eissenberg have drawn comparisons between cigarettes, ST, and NRT with regard to "difficulty quitting" as a marker of dependence (Fagerstrom & Eissenberg, 2012). In their systematic review of cessation studies, the authors identified an approximately twofold higher rate of cessation (minimum six-month follow-up) in ST users compared with cigarette smokers. Cessation rates ranged from 9.8 % to 11.2 % in cigarette smokers and from 19.1 % to 33 % in ST users. In addition, Zhu et al. (2009) reported threefold higher quit rates in ST users than in cigarette smokers (38.8 % versus 11.6 %, $p < 0.001$), and that ST users are more likely to quit after behavioral interventions relative to exclusive smokers or dual users (Burton et al., 2009; Morgan, 2001). Additionally, withdrawal signs and symptoms in ST users are similar to those reported in smokers, but the magnitude of withdrawal appears to be lower in ST users.

Overall, the available published evidence suggests that the abuse liability of ST is lower than that of cigarettes and higher or similar to that of NRT. 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 or more reinforcing than NRT products.

6.3.8.2.1. Summary

The scientific literature supports a conclusion that ST users, in general, have milder withdrawal signs and symptoms and higher cessation rates compared to cigarette smokers. Overall, the literature suggests that the level of dependence is similar, or lower, in ST users than in cigarette smokers.

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[20] Institute of Medicine, 2012. Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, DC: The National Academies Press, at 7.

6.3.8.3. Misuse and Abuse of ST

Tobacco products in general, including ST products like MST, have a long, established history of use in the U.S. Very little relevant literature exists on the misuse and abuse[21] of ST. For the purpose of this analysis, we characterized misuse/abuse of ST as any use outside of "normal use," which is placement of the manufactured product in the oral cavity.

Only a few cases of intentional misuse of ST products appear in the literature, including making concentrated extracts for folk remedies, or attempting suicide (Garcia-Estrada & Fishman, 1977; O'Berst & McIntyre, 1953; Schneider et al., 2010; Willis, 1937). With the exception of one report (Edwards, 1987), the source of the tobacco (i.e., ST or smoking tobacco) is not readily discernible from the reports. Within the current literature, only a few case reports exist that describe using dry snuff to brush teeth (Edwards, 1987), as folk remedies for various health conditions (Garcia-Estrada & Fishman, 1977; O'Berst & McIntyre, 1953; Willis, 1937), or intentionally committing suicide by ingesting a concentrated extract (Schneider et al., 2010).

Given that the candidate product has been marketed for many decades and billions of cans of MST have been sold, the paucity of reports suggests that misuse and abuse of ST products are historically quite rare. We expect that the proposed modified risk claim for the candidate product would not alter this finding.

6.3.8.4. Overall Summary

We summarize the abuse potential of the candidate product on three sources of evidence:

- The clinical study demonstrates that the nicotine pharmacokinetics, subjective effects and *ad libitum* product use behavior of the candidate product are relatively lower compared to cigarettes and higher or similar compared to nicotine polacrilex gum;

- Our review of the literature indicates that the dependence potential of U.S MST products, and ST products in general, is relatively lower compared to conventional cigarettes; and

- We expect that the proposed modified risk claim for the candidate product should not result in an increase in misuse and abuse, since historically there is a paucity of reports of ST on this topic.

We conclude based on our assessment that the abuse potential of the candidate product is lower than cigarettes and greater or similar to NRT products, specifically nicotine polacrilex gum.

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[21] For pharmaceutical products, misuse refers to using a drug in excessive quantities or using a drug for purposes for which it was not intended (World Health, O. (1994). Lexicon of Alcohol and Drug Terms Published by the World Health Organization. Retrieved from http://www.who.int/iris/handle/10665/39461. Abuse refers to the "maladaptive pattern of drug use leading to clinically significant impairment or distress, such as recurrent substance use in physically hazardous situations, and continued use despite persistent or recurrent social/interpersonal problems caused by the effects of the drug" (Diagnostic and Statistical Manual of Mental Disorders, Text Revision).

6.3.9. Overall Conclusions

Misunderstandings about the relative health risks of tobacco products can contribute to a progression of tobacco use from less harmful ST products toward the more harmful activity of cigarette smoking. We believe that an accurate modified risk claim delivered to tobacco consumers, particularly adult cigarette smokers or dual users who wish to stop smoking, but continue to use tobacco, can change perspectives and alter current trends. We expect, however, that this transition is not likely to take place immediately after a single exposure to a modified risk message. As suggested by other researchers, repeated exposures would likely be needed in order for the information to permanently alter beliefs, intentions, and to have any sustained influence on tobacco use behaviors (Borland et al., 2012).

Predicting the likelihood of some behavioral changes is difficult, particularly given deeply rooted misperceptions. While we provide some perspective on possible behavior changes for current tobacco consumers in this application, our proposed postmarket surveillance program (Section 8.1) will provide additional information on the likelihood of use under real world conditions.

With regard to likelihood questions posed by FDA, we provide the following conclusions:

- **The likelihood that current tobacco product users will start using the product.**

Results of our CCI Study indicate a minimal increase in likelihood of using the candidate product among current tobacco product users. A subgroup of adult male smokers expressed increased interest in using the product, serving as the basis for the population model. We anticipate that (1) emphasis on "complete switching," (2) accurate communication of the reduced risk of lung cancer in our modified risk claim, and (3) prolonged exposure to modified risk claim will encourage ATC to start switching to the candidate product over time. Switching to the candidate product will most likely be observed among ATC who already use MST (either exclusive use or dual use), or among AS who are open to alternate tobacco product use. Current MST users or dual users appear to be generally more receptive to candidate product use as compared to smokers. Even among these groups, however, after a single exposure to the proposed claim, initial interest is low.

- **The likelihood that tobacco users will switch to or switch back to other tobacco products with higher levels of risk.**

The published literature is clear that tobacco users consume tobacco products for many reasons. Compared with never-users of tobacco, ST use could be associated with an increased probability of cigarette smoking; ST use, however, does not appear to cause cigarette smoking.

It is difficult, if not impossible, to estimate, in a pre-market setting, the impact of the modified risk claim on the likelihood of transitioning between and among tobacco product use states over time. We do not anticipate that current MST users who adopt the candidate products would switch to smoking at any accelerated rate, particularly as they become aware of the accurate risk differential between the candidate product and cigarettes. Some current tobacco users (i.e., smokers) will, however, dual use or alternate between tobacco products as part of a transition over time to the candidate product.

- **The likelihood of dual use with other tobacco products.**

Our proposed modified risk claim emphasizes complete switching; however, immediate adoption of the candidate product is not likely to occur. As consumers transition from the use of cigarettes to the candidate product, some level of dual use may occur during this transition period. Currently, we cannot predict the duration of the transition period. Ultimately, a smoker's beliefs and motivations will determine the success and length of a transition to lower risk products. Considering the fewer serious health risks associated with ST use as compared with cigarette smoking (Section 6.1), providing AS with truthful and accurate information about the candidate product could facilitate this transition. Our proposed postmarket surveillance (Section 8.1) plan will provide the agency with additional information related to dual use of the candidate product with other tobacco products.

- **The likelihood that users who may have otherwise quit using tobacco products will instead use the product.**

The current scientific evidence does not lead us to conclude that marketing the candidate product with the proposed modified risk claim would hinder smokers' attempts to quit smoking. Our consumer study assessing the possible impact of the candidate product and the associated modified risk claim on cessation intentions indicate little reason to believe that smoking cessation trends would be adversely impacted. We anticipate that our proposed modified risk claim message would accelerate smoking cessation among those who adopt the product.

- **The likelihood that consumers will use the product as intended or designed.**

MST product use has been well established over decades and is traditionally used orally. Familiarity with MST products among tobacco consumers and the long history of use lead us to conclude that inclusion of the claim language will not result in a remarkable change in current use. We expect future tobacco consumers (including those only familiar with cigarettes) will use the candidate product as MST consumers have for decades.

- **Abuse potential**

The abuse potential of the candidate product is lower than cigarettes and greater than, or similar to, that of NRT products, based on its pharmacokinetic profile and subjective effects measured in our study and the published literature. These findings can be interpreted in the context of the recommendations made by the Institute of Medicine (IOM) Committee on Scientific Standards for Studies on Modified Risk Tobacco Products (commissioned by FDA):

> "[t]he MRTP should be somewhat more reinforcing than nicotine replacement therapies but perhaps less reinforcing than conventional cigarettes. Ideally, an MRTP would be sufficiently reinforcing so as to attract smokers away from conventional cigarettes but not enough to encourage the widespread dependent use of the product by individuals who were previously nonusers, or who would have quit smoking."

In sum, abating the IOM Committee's concern, we have no indication that the candidate product will "encourage widespread dependent use of the product by individuals who were previously non-users or who would have quit smoking."

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