6.5.: POPULATION MODEL RESEARCH SUMMARY

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6.5. POPULATION MODEL RESEARCH SUMMARY

6.5.1. Introduction

The Food, Drug and Cosmetic Act states in Section 911(g)(1) that for issuance of a modified risk order, the applicant must demonstrate that Copenhagen® Snuff Fine Cut[1] (candidate product), as it is actually used by consumers, will:

> ‘‘(A) significantly reduce harm and the risk of tobacco related disease to individual tobacco users; and
>
> (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.”

In Section (VI)(B)(4) of its Modified Risk Tobacco Product Applications (MRTPAs) Draft Guidance (2012), the Food and Drug Administration (FDA) acknowledges “[t]he difficulties inherent in making premarket assessments of the effect that the introduction of an MRTP [modified risk tobacco product] would have on the population as a whole and the public health.” Further, the Draft MRTPA Guidance states that “[a]pplicants may opt to use currently available models in the scientific literature to forecast the harm to public health from tobacco use.”

In this section, we summarize our population impact assessment of a potential market order for the candidate product based on a computational model. Altria Client Services LLC (ALCS) developed this model, the ALCS Cohort Model, in collaboration with Edward Boone, Ph.D., Associate Professor at Virginia Commonwealth University. Dr. Boone’s expertise is in employing Bayesian methodologies, hierarchical models, and uncertainty quantification for ecological, environmental, and health applications. During development of input parameters and analysis of modeling outcomes, we also relied on the expertise of Professor David A. Swanson, Ph.D., from University of California Riverside. Dr. Swanson has served as a member of the U.S. Census Bureau’s Scientific Advisory Committee for six years and chaired the group for two years. Section 7.4.2 details the ALCS Cohort Model, which is also described in a poster by Boone et al. (2016). This section provides an integrated quantitative assessment of the net benefit of introducing the candidate product with a modified risk claim to the population of users and nonusers of tobacco products in the U.S.

6.5.1.1. Background

In recent years, several mathematical models have assisted in predicting the potential public health impact of change in use of tobacco products with varying levels of inherent risk.

[1] 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.

Bachand et. al (2013) and (2017) used cohort-based compartmental models to assess the introduction of an MRTP on all-cause mortality. Vugrin et al. (2015) utilized a multistate, dynamic systems population modeling structure to assess the potential impact associated with use of a variety of tobacco products. Weitkunat et al. (2015) and Lee et al. (2017) used a Markov model combined with a negative exponential mortality model to estimate the effect of introducing a reduced risk MRTP on a hypothetical U.S. population sample of 10,000 individuals. Hill et al. (2016) and (2017) used a system dynamics based compartmental stock and flow model to assess the potential health impact of launching a new MRTP into the marketplace and to reinforce their views that e-cigarette use is likely to benefit United Kingdom population health. Levy et al. (2016) applied a decision-theoretic model to estimate the public health impact of introducing vaporized nicotine products such as e-cigarettes in the U.S. Cherng et al. (2016) applied agent-based modeling techniques to examine hypothetical scenarios of e-cigarette use by smoking status and the effect of e-cigarette availability on smoking initiation and smoking cessation. Poland et al. (2017) developed a statistical model to explore the effect on population mortality of an MRTP introduction resulting in reduced conventional cigarette smoking.

ALCS has developed the Cohort Model (Section 7.4.2), using similar principles as described in the literature, "to forecast the harm to public health from tobacco use." This model uses best practices described by the Modeling Good Research Practices Taskforce, a joint task force developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM), for the development of mathematical models for health care and public health decision-making (Caro, Briggs, Siebert, & Kuntz, 2012).

The published guidelines also provide details about parameter estimation and uncertainty, including documenting data sources, data quality, and estimation processes used to obtain input parameters for the model. The guidelines describe various forms of uncertainty analyses related to inputs and their effect on the model (Section 6.5.7).

6.5.1.2. ALCS Cohort Model Introduction

We developed our own model, because the models in the literature are not publicly available for use and each model is bound by the developers' assumptions and particular outcomes of interest. The ALCS Cohort Model (Boone et al., 2016) (Section 7.4.2) was developed and validated following the key elements proposed within the ISPOR-SMDM published guidelines mentioned in Section 6.5.1.1. Furthermore, the ALCS Cohort Model aligns with the ISPOR-SMDM best practices at each step and makes reasonable assumptions when needed. Section 6.5.4 discusses the main assumptions and their impact on the modeling conclusions.

The ALCS Cohort Model estimates the overall health impact from the introduction of the candidate product by comparing the survival of hypothetical populations in two scenarios:

1. Base Case Scenario – This *status quo* scenario takes into consideration the transitions within the male U.S. population under the existing tobacco product use behaviors for cigarettes and moist smokeless tobacco (MST) products.

2. Modified Case Scenario – This scenario reflects a future state in which the transitions within this population change in the presence of both cigarettes and MST products available with the proposed claim.

In order to estimate the impact on the U.S. population of market authorization of the candidate product with the proposed modified risk claim:

1. We first estimate the impact at the MST category level by determining the number of lives saved in a single cohort of one million males starting at age 13 years. We focus on males as they represent ~ 95% of adult MST users, according to the 2014 National Survey on Drug Use and Health [NSDUH (2016)].
2. Second, we estimate the number of lives saved in a representative, U.S. native-born male population by extending the single-cohort model to a time-staggered, multi-cohort model. These estimates are based on the *category level*, because the transitions within the male U.S. population are determined from category-level information.
3. Third, we obtain the number of lives saved from market authorization of *the candidate product* by scaling the category level estimates of the number of lives saved. We use the current market share of the candidate product to adjust the category level estimates from the multi-cohort model, since the candidate product's impact on the population can only be derived from the category level estimates.

The ALCS model is unique in several aspects:

- The Base Case Scenario takes into consideration the tobacco use behaviors in the population for both cigarettes and MST, the most predominant forms of tobacco products and relevant to this application. Further, the long histories of use for these tobacco products provide reliable transition probabilities.
- We use a staggered, multi-cohort approach that provides relatively more realistic estimates of net benefit to the native-born male U.S. population.
- We estimate the net benefit of FDA authorization of the proposed claim for the candidate product based on current market share. Unlike new tobacco products, market share data for Copenhagen® Snuff Fine Cut is both realistic and reliable, as the candidate product has been marketed for decades.

Details for the single-cohort and the multiple-cohort analysis are provided in Section 7.4.2. We also provide justification for our population of interest (i.e., the U.S. native-born male population) in Section 7.4.2.2.3.

6.5.1.3. Modeling Results Demonstrate Net Benefit to U.S. Population

At the category level, the ALCS Cohort Model results demonstrate a net positive benefit to the U.S. population through both the single-cohort and multi-cohort modeling approaches. The key findings of the single-cohort modeling approach include the following:

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

Similarly, the time-staggered, multi-cohort approach predicts:

- 93,000 additional survivors among the U.S. native-born male population after a follow-up period of 60 years.

With respect to the candidate product, to better approximate the net population benefit gained by authorizing the proposed claim, we scale multi-cohort model results using the candidate product's current market share. We believe that extending the model specifically to the candidate product reflects a more realistic scenario. The key findings include:

- 7,500 additional survivors among the U.S. native-born male population after a follow-up period of 60 years following market authorization of the candidate product with the proposed claim.

We have made a conservative assumption that the market share of the candidate product would remain the same for 60 years after authorization of the proposed claim. Tobacco product use behavior is dynamic, and many factors could influence the transition from cigarettes, such as availability of the accurate risk information for the candidate product. As adult consumers permanently alter their beliefs and misperceptions regarding the candidate product, we expect changes in tobacco product use behavior accompanied with accelerated transition from cigarettes to the candidate product. The potential changes in tobacco use behavior will likely result in a greater number of lives saved than the current projected net benefit to the population. We intend to update our predictions as postmarket surveillance data becomes available.

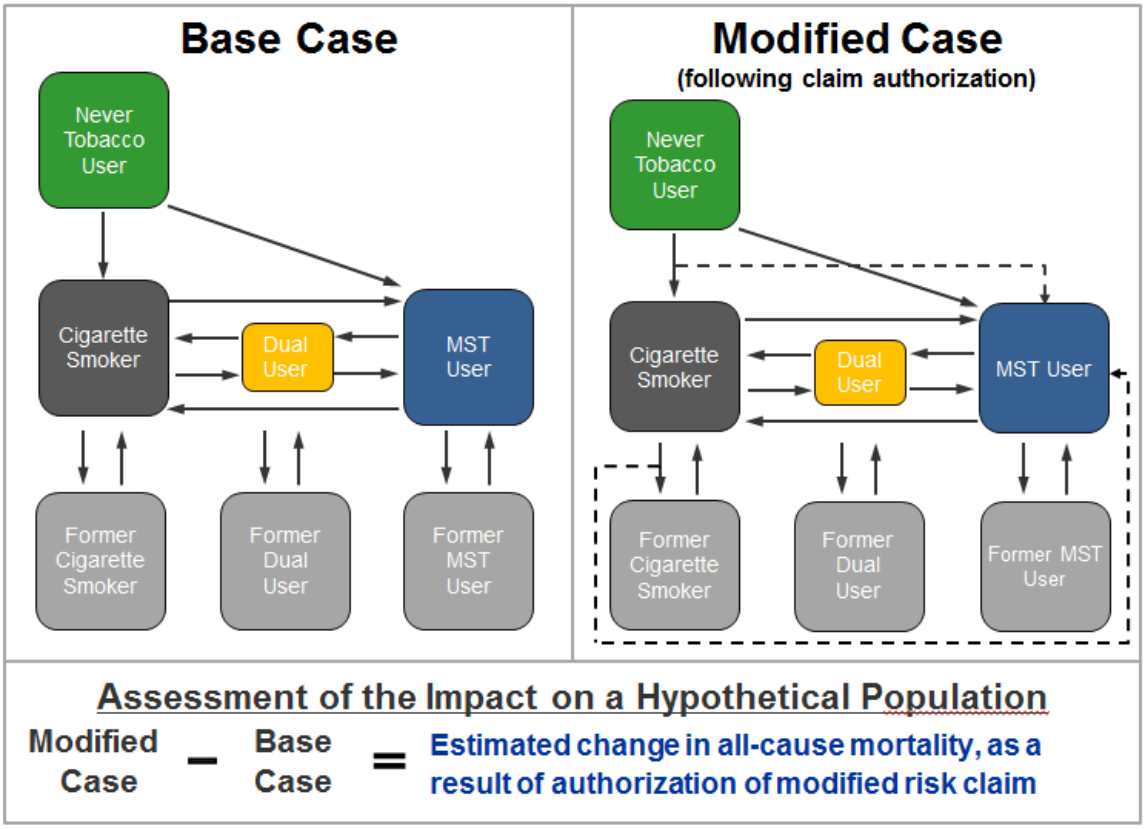
6.5.2. ALCS Cohort Model Framework

6.5.2.1. Base Case and Modified Case Scenarios

The ALCS Cohort Model uses a hypothetical population to assess the overall difference in all-cause mortality between Base Case and Modified Case scenarios.

Following published modeling best practices (Section 6.5.1.1), we present a framework which includes 30 potential transitions within a compartmental model (see Figure 6.5-1, a simplified version) that estimates the net benefit when market authorization is received for a modified risk claim, by comparing a Base Case scenario with a Modified Case scenario. This model structure is similar to the one adopted by Bachand et al. (2013). The detailed compartmental model with the states, transitions, and transition probabilities is illustrated in Section 7.4.2; Figure 7.4.2-4, along with detailed explanations of what each transition represents in Section 7.4.2; Table 7.4.2-4 and Table 7.4.2-5.

Figure 6.5-1: Modeling Effect of Authorization of a Modified Risk Claim on an Existing MST Product



Note: The actual ALCS Cohort Model consists of 29 states and 30 transitions (Section 7.4.2; Figure 7.4.2-4).
MST = moist smokeless tobacco.

In this framework, our Base Case (status quo) assumes cigarettes and MST already coexist in the marketplace. In the Modified Case Scenarios, these products still coexist, but the use behavior is altered due to the modified risk claim. A Modified Case scenario is defined as one in which at least one transition probability is changed from the Base Case scenario. The Master Case is a special adaptation of the Modified Case scenario, reflecting a combination of our most likely estimates for each of the transition rates. Thus, it represents our most likely outcome of authorization of the proposed claim.

6.5.2.2. Estimating Differences Between Scenarios

The ALCS Cohort Model estimates the survival of hypothetical populations in the Base Case and Modified Case scenarios with two approaches:

1. a single-cohort approach that estimates the survival of a hypothetical cohort population of 1,000,000 males at five-year intervals, starting from the age of 13 years and followed to the age of 73 years; and
2. a time-staggered, multi-cohort approach that estimates the survival of the native-born, U.S. male population by starting a new cohort, with ages from 0 to 4 years, every five years until the population is comprised of ages from 0 to 84 years.

We employ a Markov compartmental model to simulate transitions between 29 mutually-exclusive, tobacco-use states (model details are presented in Section 7.4.2). Transition probabilities (i.e., demographic- and product-specific probabilities of either remaining in the same state or transitioning from one state to another) are used to propagate the population through the various states over time. The Markov model is coupled with mortality models developed using data from a Kaiser-Permanente Medical Care Program Cohort study (Friedman, Tekawa, Sadler, & Sidney, 1997) (details presented in Section 7.4.2.1). The statistical mortality models are combined with excess relative risks (ERRs), as described in Section 7.4.2.2.1, to determine the survival probabilities of the population at the end of each time step, as described in Section 6.5.2.1, to compare survival between the Base Case and Modified Case scenarios.

6.5.2.3. Outputs of the Model

We present the survival outputs of the model as demographic life tables for the Base Case and the Master Case, which is the most likely Modified Case scenario outcome if the proposed claim is authorized (see Sections 6.5.2.1 and 6.5.6.4 for descriptions of the Base, Modified, and Master Case scenarios). The modeling output tables display two key metrics: l_x (the expected number of survivors at each age group,x) and T_x (the cumulative number of years of life lived by the survivors at each age group,x).

We first present results comparing number of survivors in the Base Case vs. the Master Case scenarios, to demonstrate that there would most likely be a net benefit to the population from the authorization of a modified risk claim. To determine the percent by which the Base Case transition rates will change in the Master Case (i.e., how users will transition between products upon authorization of the proposed claim), we estimate the percent difference between the relevant response of a Test group (exposed to an advertisement with the modified risk claim) and Control group (exposed to an advertisement without the modified risk claim) in the ALCS Claim Comprehension and Intentions Study (CCI) Study (Appendix 7.3.2-1). We then apply the percent difference to the nationally representative Base Case transition rates obtained from studies referenced within Tam et al. (2015). Details are discussed in Section 6.5.6.4 and Section 7.4.2.2.4.

We then conduct three sets of analyses in which we compare a series of Modified Cases to the Base Case. In the *first* set, we modify the point estimate transition probability of only one transition rate at a time in the Modified Case, while keeping all other transition rates the same as those in the Base Case. This set of analyses involves seven scenarios, allowing us to understand the contribution of each individual transition to the observed total net benefit. Details are discussed in Section 6.5.7.4 and Section 7.4.2.3.3.

In the *second* set of sensitivity analyses, we evaluate the effects of varying input parameters and the related assumptions. For each transition, we systematically vary the parameter used for that transition in the Master Case (obtained from the ALCS CCI Study, Appendix 7.3.2-1), from 0 (i.e., no change) to 2 times (two-fold increase) its value, while holding all other values the same as those in the Base Case. Details are discussed in Section 6.5.7.5 and Section 7.4.2.3.4.

In the *third* set of analyses, discussed in Section 7.4.2.3.4, we conduct a sensitivity analysis by building a host of additional Modified Case scenarios. In each case, we change one transition rate at a time, while keeping all other transition rates in the Modified Case the same as those in the Master Case. For each transition, we run scenarios in which we increase and decrease the Master Case transition rates.

6.5.3. Compartmental Model Overview

Compartmental models can be used to show discrete states as categories in which an individual may reside. At any time, an individual may reside in one and only one state (including death, a terminal state) with the probability of remaining in the same state or moving to a different state at the next time point. A compartmental model estimates the individual's transition between states through time (discussed in detail in Section 7.4.2.1.1).

6.5.3.1. Markov Chain Approach

We implemented the Markov chain approach beginning with a hypothetical cohort of 1,000,000 subjects of the same sex (male), with survival estimated in five-year intervals, starting from age 13 years. The membership of each of the following basic states was considered:

- never-user of tobacco;
- current cigarette smoker;
- former cigarette smoker;
- current MST user;
- former MST user;
- dual user (current cigarette smoker and current MST user); and
- former dual user (both former cigarette smoker and former MST user, but currently uses neither product).

6.5.3.2. Modeling Transitions

To estimate whether an individual (cohort member) belongs in a specific state we considered transition paths between states listed in Section 6.5.3.1. To describe the most plausible pathways by which a cohort member could progress through the model, we employed 29 states and specified 30 transition probabilities. An illustration depicting the states, transitions, and transition probabilities for our Markov chain compartmental model can be found in Section 7.4.2, Figure 7.4.2-4.

6.5.4. Single Cohort Model: Model Validation, Assumptions, and Limitations

The ALCS Cohort Model approach uses a cohort-based, Markov chain transition integrated with mortality models developed to predict public health outcomes associated with tobacco products. At each juncture in the ALCS Cohort Model's development, quality control measures, sensitivity analyses, uncertainty analyses, model verification, and model validation were used to ensure the model's fit for use and prediction ability.

6.5.4.1. Validation of Single Cohort Approach

The ALCS Single Cohort Model has been verified and validated to estimate public health outcomes (i.e., changes in all-cause mortality) by comparing the modeling predictions for a cohort of U.S. male and female populations against the number of survivors estimated using mortality data reported in the U.S. Life Table from the Centers for Disease Control and Prevention (Arias, 2010). The male and female populations were run separately as cohorts. The percentage difference between the age-specific mean number of survivors predicted by the model and the age-specific mean number of survivors estimated by Centers for Disease Control and Prevention is less than 4 percent for both the U.S. male and female populations. The results in Section 7.4.2 (Table 7.4.2-8, Table 7.4.2-10, Table 7.4.2-12) and Section 6.5.5.2 indicate that the model is fit for use and predicts survival well across both sexes. Though validated for both genders, for scenario analysis in this MRTPA, we run the model only for the male populations, as historical data show that MST is predominantly used by males, has an extremely low prevalence among the female population, and that this trend has remained consistent over time.

6.5.4.2. Model Assumptions

At each step of the model development and analysis, efforts were made to use both reasonable assumptions and model parameter estimates. While some assumptions in the model are explicitly assumed (such as ERR values and transition probabilities), others are implicit and are summarized below:

- A key assumption is that the Kaiser-Permanente data set used to create the mortality models is representative of the general population. However, the study participants had health insurance, short follow-up periods, and their age-specific mortality rates were lower than those for the U.S. population (Friedman et al., 1997). We, therefore, have adjusted the dataset by assigning weights that reflect mortality rates in the U.S. population (Section 7.4.2.1.3; Table 7.4.2-1). We note that, apart from the Kaiser-Permanente data set, very few publicly available data of this nature exist in the literature, especially with the attributes of "number of years smoked" and "years since cessation" and their impact on all-cause mortality. A similar approach has been published in peer-reviewed literature, Bachand et al. (2013).
- We assume that the mortality risks associated with the model's variables (i.e., age, years of smoking, years since quitting, and relevant interaction terms) are appropriately specified. Although these models seem to fit the data well, there is

some evidence of overfitting, which is expected with complex models (Section 7.4.2.2.7).

- Although numerous transitions states can possibly occur, we assume that the 29 states are sufficiently specified to account for all reasonable paths of use over time. These 29 states in the model allow for people to switch between products, as well as to cease product use (discussed in detail in Section 7.4.2.1.5).
- We assume that the changes to transition rates from the ALCS CCI Study (Appendix 7.3.2-1) will remain approximately constant over the modeling time period. Similarly, we also assume that the product-specific initiation, cessation, and other transition rates do not change over the modeling time period and that age- and product use state–specific mortality rates remain constant over the modeling time period. We plan to refine the model prediction estimates as new data become available through the postmarket surveillance studies.
- Poly-tobacco use (e.g. e-cigarette use) is common among many adult tobacco consumers [PATH (2017)]; however in order to limit the transitions to a manageable number we did not include all other tobacco products. Furthermore, we assume that much of the poly-tobacco use is occasional; thereby not impacting the health effects as much as regular use of cigarettes.

6.5.4.3. Model Limitations

ALCS has also identified three limitations of the ALCS Cohort Model:

- The temporal resolution of the compartmental model is five years. Hence, it cannot adequately account for participant transitions occurring within a five-year period (e.g., an individual who initiates cigarette smoking in the first year, quits smoking, and switches to MST in the second year, quits MST and returns to cigarette smoking in the fourth year, and quits smoking in the fifth year). The model will assign this participant the same risk as someone who smoked almost the entire five-year span and stopped using cigarettes right before the next transition (discussed in detail in Section 7.4.2.2.7). We believe that this limitation should not impact the mortality outcomes significantly as most tobacco-related diseases manifest from chronic use of the product over several decades.
- Two subpopulations – “Would-be Smoker” and “Would-be Smoking Quitter” (see Table 6.5-5) – that may be impacted by authorization of a modified risk claim could not be studied in the ALCS CCI Study (Appendix 7.3.2-1) because of the impracticality of assessing these transitions in a pre-market survey setting. Therefore, we conduct a sensitivity analysis using a wide range 0%-100% (Case 3, Section 7.4.2; Table 7.4.2-39 for Would-be Smoker and Case 5, Section 7.4.2; Table 7.4.2-43 for Would-be Smoking Quitter) of transition probabilities and determined that the assumptions were reasonable.
- Also limiting the single cohort approach is that the inferences are somewhat tied to the homogeneous cohort group, which limits generalizability to the population, which

is inherently more heterogeneous in nature. The multiple-cohort modeling approach discussed below helps address this limitation.

6.5.5. Multiple-Cohort Modeling

6.5.5.1. Rationale for Multiple Cohorts

Single-cohort models are designed to take a specific homogeneous group and track it through time using defined transition probabilities and mortality rates. As discussed in Section 7.4.2, single-cohort modeling is useful for determining the influence of an intervention. In Section 7.4.2.1.10, we propose and discuss a methodology to minimize the limitation of a homogenous cohort group and allow inferences to a more heterogeneous population by employing a time-staggered, multiple-cohort approach. In this approach, we use a series of individual cohorts, wherein each individual cohort is as homogeneous as possible; however, because each cohort is unique and different, using multiple cohorts allows heterogeneity in the overall population. Grouping via multiple cohorts will, thus, provide the ability to extend inferences to U.S. native-born males, the population most likely to be impacted by authorization of the proposed claim. We limit scenario analysis to U.S. males for this MRTPA based on historical data showing very low prevalence of MST consumption among females (Section 7.4.2.1.10).

6.5.5.2. Validating the Multiple-Cohort Approach

We used the multiple-cohort approach to build a population of U.S.-born males living in the year 2015 with ages ranging from 0 to 104 years. Since our single-cohort model operates in five-year intervals, we initiated the first cohort of ages 0 to 4 years in the time period 1910 to 1914 and modeled the survival of that single cohort over a period of 104 years up to the year 2015. Survivors from this single cohort represent males who are 100 to 104 years of age in the 2010 to 2014 time period. Similarly, we followed this approach multiple times to populate the number of survivors in all the age groups for the period 2010 to 2014.

We validated the approach by comparing the total population (0-104 years of age) generated by the multiple-cohort modeling approach to that reported by the U.S. census in 2015. Comparison shows a 2.22 percent difference between the populations generated using our multiple-cohort modeling approach and the estimate reported in the U.S. census data for the 2015 U.S. native-born male population (i.e., 140,297,321 model estimate vs. 137,187,000 U.S. Census Bureau). Section 7.4.2.1.10 provides the modeling details.

We further validated the multiple-cohort approach by comparing model population estimate projections with U.S. native-born male population projections from the U.S. Census Bureau for the 2015 to 2060 timeframe. The comparison revealed less than a 6 percent difference between the two projections (more details can be found in Section 7.4.2.1.10).

The comparisons between our modeling result and the U.S. Census data show that using the single-cohort models in a multiple-cohort setting with a time-staggered structure, as described in Section 6.5.5.1, can successfully model the U.S. native-born male population. Furthermore, the validation of this approach shows that our model can generate age distributions and be used for scenario testing of interventions (e.g., authorization of the

proposed claim). The validation of our multiple-cohort model approach also further validates our single-cohort model.

Therefore, we conclude that the ALCS Cohort Model, employed both in a single-cohort setting and in a multiple-cohort setting, is a valid and useful tool for predicting public health outcomes (i.e., all-cause mortality) driven by behavioral changes that may occur if the proposed claim is authorized.

6.5.6. Population Model Inputs

Outcomes of the ALCS Cohort Model depend on several key inputs that include but are not limited to:

- estimation of Excess Relative Risk (ERRs) (detailed in Section 7.4.2.2.1);
- transition probabilities between different tobacco use states such as never-use of tobacco, cigarette smoking, MST use, and dual use (cigarette smoking and MST use) (detailed in Section 7.4.2.2.2); and
- estimated impact of authorization of the proposed claim on the transition probabilities (detailed in Section 7.4.2.2.4).

Performing uncertainty, sensitivity, and other statistical analyses adds validity to the results (described in Section 7.4.2.3).

6.5.6.1. Excess Relative Risk (ERR)

In the context of this MRTPA, ERR is the excess relative risk from using ST compared to cigarettes. We estimated Cox proportionality mortality hazard ratios from smokeless tobacco (ST) use or cigarette smoking based on two nationally representative, cross-sectional public health surveys linked to prospective mortality follow-up data (Section 7.4.1). For modeling purposes, we derived the ERR of current ST users relative to current smokers based on the all-cause mortality hazard ratio estimates for the two populations (described in detail in Section 7.4.2.2.1).

The baseline ERR for never-users of tobacco is 0.0, whereas the baseline ERR for current cigarette smokers is 1.0. In this context, we estimated the ERRs of current ST users compared with those of current cigarette smokers and the ERRs of former ST users compared with those of former cigarette smokers. This calculation and its basis are presented in Section 7.4.2.2.1 of this MRTPA. In addition, we assigned the mortality risk of dual use of cigarettes and ST to be the same as the mortality risk of exclusive cigarette use, based on findings and results from published literature (Accortt, Waterbor, Beall, & Howard, 2002; Frost-Pineda, Appleton, Fisher, Fox, & Gaworski, 2010) and findings from the ALCS Linked Mortality Analysis (Appendix 7.4.1-1).

The ERR of current ST users compared with that of current cigarette smokers is estimated to be 0.09, and the ERR of former ST users compared with that of former cigarette smokers is estimated to be 0.04. For example, the interpretation of the 0.09 value is that exclusive ST use is 91% less risky than exclusive cigarette smoking. Calculation details are presented in Section 7.4.2.2.1 of this MRTPA.

6.5.6.2. Base Case Transition Probabilities from Literature

The ALCS Cohort Model is a compartmental model that requires estimation of 30 transition probabilities that allow for moving the population between 29 current and former MST use states; current and former cigarette smoking states; the never–user of tobacco state; and a terminal state (mortality). Tam et al. (2015) summarized the ST-related transition probabilities in a systematic review of published literature on transitions between ST use and cigarette smoking in the U.S. The review discussed six studies, from which we selected three relevant studies to estimate our transition rates (Tomar, Alpert, & Connolly, 2010; Wetter et al., 2002; Zhu et al., 2009). For generating transition probabilities used in the Base Case scenario of the model, we selected these three studies because the underlying populations were the most generalizable to the U.S. population, and the transition time periods were most similar to those used in our modeling analyses (discussed in detail in Section 7.4.2.2.2).

6.5.6.3. Impact on the Population as a Whole

In its MRTPA Draft Guidance (2012), the FDA recommends that manufacturers address the effect of an MRTP on the population as a whole and make quantitative estimates of the effect of marketing the product on the health of the population as a whole, including current tobacco product users and nonusers.

Among *current tobacco users*, these effects include the likelihood that:

- they will start using the candidate product;
- after adopting the candidate product, they will switch to or switch back to other tobacco products that present higher levels of individual health risk;
- they will use the candidate product in conjunction with other tobacco products; and
- those who may have otherwise quit using tobacco products will instead use the candidate product.

Among *current nonusers of tobacco products*, these effects include the likelihood that:

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

Section 7.4.2; Table 7.4.2-19 summarizes the alignment of user group definitions between the populations of interest discussed in the MRTPA Draft Guidance and populations surveyed within the ALCS CCI Study.

Several of the relevant transitions discussed above and their effect on the population as a whole (e.g., overall change in all-cause mortality between the Modified Case and Base Case scenarios) are discussed in aggregate and individually in Section 7.4.2.3.

6.5.6.4. Estimates from the ALCS CCI Study

As previously discussed, our population model employs three types of scenarios:

1. The Base Case, the world as we know it today, is composed of nonusers of tobacco products, cigarette smokers, and MST users with transitions between these states.
2. The Modified Cases represent a range of scenarios that would be possible with the authorization of the proposed claim. While ALCS has sought to identify the most likely modified case (i.e., the Master Case described in the third class), we are aware of the potential vulnerabilities of the model predictions if the real-life transitions deviate from expectations. To account for this, we present sensitivity analyses in Section 6.5.7.5 and Section 7.4.2.3.4 for each of the seven transitions affected by proposed claim.
3. The Master Case is a special adaptation of the Modified Case category, reflecting a combination of our most likely estimates for each of the transition rates. Thus, it represents our most likely outcome of authorization of the proposed claim. For the Master Case, we estimated the percent difference between the relevant response of the test group (exposed to an advertisement with the proposed modified risk claim) and control group (exposed to the advertisement without the proposed claim) in the ALCS CCI Study (Appendix 7.3.2-1) and then applied the percent difference to the nationally-representative Base Case transition rates obtained from studies referenced within Tam et al. (2015) to generate the corresponding transition rates for the Master Case scenario.

Section 7.4.2.2.4 details this methodology. Table 6.5-1 below summarizes the change in responses in the ALCS CCI Study (Appendix 7.3.2-1) with and without claim exposure that were used to estimate the percent change between transition rates used for the Master Case vs. the Base Case scenario.

Table 6.5-1: Likelihood of Use with and Without Claim from ALCS Claim Comprehension & Intentions Study

			Column A	Column B	Column C	Column D	Column E[1]
Section	**User and Non-user Groups**	**Intended Behavior**	**Control Group without Ad Exposure**	**Control Group with Ad Exposure**	**Test Group without Claim Exposure**	**Test Group with Claim Exposure**	**Relative Percentage Change**
Nonusers Who Initiate Tobacco Use with the Proposed Product, Never-Users, and Former Users *"MRTP Initiation"*							
7.4.2.2.4.1	Never-user of tobacco (ever-past trier/never-trier)	Initiate Candidate Product	0.031	0.024	0.048	0.036	-4.8%[2]

			Column A	Column B	Column C	Column D	Column E[1]
Section	**User and Non-user Groups**	**Intended Behavior**	**Control Group without Ad Exposure**	**Control Group with Ad Exposure**	**Test Group without Claim Exposure**	**Test Group with Claim Exposure**	**Relative Percentage Change**
	Former MST user		0.031	0.000	0.073	0.035	0.0%
	Would-be smoker		NA				+1.0%
Tobacco Users and Nonusers Who, after Adopting the Proposed Product, Switch … *"MRTP to Smoking"*							
7.4.2.2.4.2	Current exclusive MST user	Switch to Cigarette	Not measured in the study				
Tobacco Users Who Switch from Other Commercially Marketed Tobacco Products to the Proposed Product *"Smoking to MRTP"*							
7.4.2.2.4.3	Current cigarette smokers (planning to quit/not planning to quit)	Switch To Candidate Product	0.177	0.159	0.140	0.151	20.8%
	Would-be Smoker quitters		NA				+5.0%
Tobacco Users Who Opt to Use the Proposed Product Rather than Cease Tobacco Use Altogether *"Smoking to Dual Use"*							
7.4.2.2.4.4	Current cigarette smokers (planning to quit/not planning to quit)	Switch to Dual (Candidate Product & cigarettes)	0.240	0.199	0.179	0.183	24.0%
Tobacco Users Who Use the Product in Conjunction with Other Tobacco Products *"Dual to Exclusive"*							
7.4.2.2.4.5	Dual users (MST and cigarette)	Switch to Candidate Product	0.341	0.324	0.355	0.356	5.7%
	Dual users (MST and cigarette)	Switch to Cigarette	Not measured in the study				

ALCS = Altria Client Services, LLC; MRTP = Modified Risk Tobacco Product; MST = Moist Smokeless Tobacco
NA = Not Available

[1] Recreating Column E from the values in the table above may not equate to the probabilities reported due to rounding. The transition probabilities in Column E are computed with the following formula:

$$\frac{\frac{Column_D}{Column_C} - \frac{Column_B}{Column_A}}{\frac{Column_B}{Column_A}}$$

[2] The relative percentage change was estimated as a negative value suggesting that exposure to proposed claim actually reduces their likelihood of initiating with the candidate product, compared to the control.

Note: (1) These values are rounded. (2) Would-be smoker initiating candidate product and would-be smoking quitter switching to candidate product are absolute percentage increases, not percentage changes. (3) Details of how the ALCS CCI study data was analyzed to obtain input data used in our modified case scenarios can be found in Appendix 7.4.2-4.

6.5.7. Population Modeling Outcomes

6.5.7.1. Outputs of Interest

Modeling results showed that there will be a positive net health benefit to the population if FDA grants market authorization of a modified risk claim for the candidate product. Our net benefit results are presented as the difference between the Base Case and Master Case scenarios, expressed using the following outputs of interest:

- the number of Base Case survivors;
- the number of Master Case survivors;
- the Base Case cumulative expected number of years remaining; and
- the Master Case cumulative expected number of years remaining.

The results (i.e., difference in number of survivors between the Base Case and the Master Case scenarios) are typically presented as point estimates, along with their 95 percent posterior credible intervals (a range of values which reflect parameter uncertainty).

To understand the contribution of each of the key individual transitions (identified from ALCS CCI Study (Appendix 7.3.2-1) and the estimated subpopulations) between behavior states to the overall net benefit observed, we compared the Base Case outcome with a series of Modified Case scenarios. We conducted Sensitivity Analysis #1 in which we constructed seven individual Modified Case scenarios by varying one of the key individual transitions of interest at a time, while keeping all other transitions static. This exercise clarified the impact (positive or negative contribution) of each individual intervention and its contribution to the net benefit observed in the comparison between the Base Case and the Master Case scenario. See Section 7.4.2.3.3 for detailed results of the individual transition rate analyses.

The ALCS Cohort Model uses multiple input parameters, each with underlying assumptions. Understanding how potential variations in input parameters could influence the model outcomes is important for understanding and interpreting the results. Section 7.4.2.3.4 presents results from Sensitivity Analysis #2, conducted by systematically varying input parameters obtained from the ALCS CCI Study (Appendix 7.3.2-1) over a wide range of potential values and evaluating their impact on outcomes of our Master Case Scenario.

6.5.7.2. Estimating Differences in Outcomes for the Single Cohort Approach

Table 6.5-2 compares modeling outcomes for the Base Case and Master Case scenarios using the single-cohort approach. As seen in Table 6.5-2, there are 676,903 survivors at age 73 followed from the initial cohort of 1,000,000 males at, age 13 in the Base Case scenario. In the Master Case scenario, there are 678,023 survivors at age 73 followed from the initial cohort of 1,000,000 males at age 13.

Table 6.5-2: Comparison of Survivors in the Base Case and Master Case

Age (y)	Master Case Scenario Life Table		Base Case Life Table		Difference (Master Case – Base Case)	
	$l_{x(m)}$ [1]	$Tx(m)$ [2]	$l_{x(b)}$ [3]	$Tx(b)$ [4]	$l_{x(m-b)}$ [5]	$Tx(m-b)$ [6]
13	1,000,000	59,914,223	1,000,000	59,881,367	0	32,856
18	997,317	58,912,882	997,317	58,880,026	0	32,856
23	993,963	53,934,688	993,963	53,901,832	0	32,856
28	989,041	48,977,188	989,036	48,944,346	5	32,843
33	981,605	44,050,596	981,594	44,017,793	11	32,803
38	970,653	39,170,002	970,627	39,137,291	26	32,711
43	954,754	34,356,594	954,680	34,324,134	74	32,461
48	932,117	29,639,644	931,920	29,607,864	197	31,780
53	902,907	25,052,474	902,538	25,022,113	369	30,361
58	865,929	20,631,030	865,346	20,603,055	583	27,975
63	818,792	16,420,329	817,980	16,395,852	812	24,477
68	757,842	12,480,710	756,831	12,460,804	1,010	19,906
73+	678,023	8,894,749	676,903	8,880,185	1,120	14,564

[1] lx(m) = expected number of survivors at the start of each age group in the Master Case
[2] Tx(m) = expected cumulative number of years of life remaining for the survivors at the start of each age group, x in the Master Case
[3] lx(b) = expected number of survivors at the start of each age group, x in the Base Case
[4] Tx(b) = expected cumulative number of years of life remaining for the survivors at the start of each age group, x in the Base Case
[5] lx(m-b) = expected number of additional survivors at each age group,x in the Master Case vs. the Base Case
[6] Tx(m-b) = expected cumulative number of additional years of life lived by the additional survivors at the start of each age group, x in the Master Case vs. the Base Case
Note: The underlying life tables extend to a final open-ended age group of 103+ years. The values shown in this table for T73+ and e73 are taken from the underlying life table.

The modeling outcomes of the Base Case and Master Case scenarios reveal two key results:

1. At age 73, there are 1,120 more survivors from the original 1,000,000 male cohort upon authorization of the proposed claim.

2. There would be 32,856 more person-years expected for the original 1,000,000 male cohort upon authorization of the proposed claim (the difference between the 59,881,367 total person-years expected for the Base Case scenario versus the 59,914,223 total person-years expected for Master Case scenario).

Because the cohort in each scenario progressively ages, the differences (net benefit) between the Base Case and the Master Case progressively increase from the age group 33 to 37 until the age group 68 to 72. Years of life gained by being in a lower relative risk state (i.e., MST use), as opposed to being in a higher relative risk state (i.e., cigarette smoking) drive the net accumulation of more years of life by those in the Master Case cohort.

6.5.7.3. Statistical Uncertainty

Uncertainty and sensitivity analyses allow us to provide a comprehensive and transparent view of the input parameters we used and also provide a means of assessing the validity of our assumptions. We detail these analyses in Section 7.4.2.3.3.

The model results are reported as the mean difference in number of survivors between the Base Case and Master Case and the corresponding 95 percent posterior credible intervals, which are formed from the 2.5 percent and 97.5 percent quantiles of 10,000 samples drawn from the posterior distribution of the parameters of interest.

Table 6.5-3 summarizes the results of the single-cohort modeling approach. The 95 percent credible interval around the mean difference of 1,120 additional survivors is 958 to 1,301 additional survivors at age 73. The 95 percent credible interval not incorporating a zero value presents a degree of statistical certainty to the modeling outcome, indicating a net benefit to the population (i.e., 958 additional survivors at the lower bound of the 95 percent credible interval).

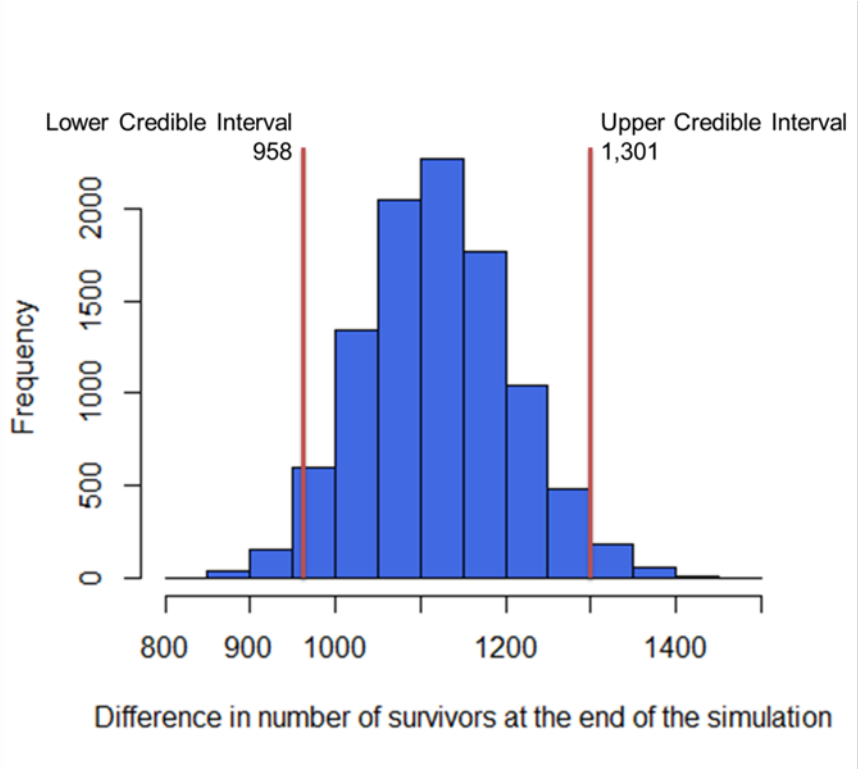
Table 6.5-3: Comparison of Survivors in the Base Case Scenario and Master Case Scenario

Age (y)	Mean Number of Survivors (Base Case)	Mean Number of Survivors (Master Case)	Mean Difference in Number of Survivors (Master Case – Base Case)	95% Credible Interval
43	954,680	954,754	74	(64, 85)
48	931,920	932,117	197	(174, 221)
53	902,538	902,907	369	(324, 417)
58	865,346	865,929	583	(507,665)
63	817,980	818,792	812	(700, 936)
68	756,831	757,842	1,010	(866, 1169)
73	676,903	678,023	**1,120**	(958, 1301)

Note: Results are reported for ages 43 through 73. In the model, survivability of the initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13.

Figure 6.5-2 shows the distribution of the estimated difference between the single-cohort Master Case and Base Case scenarios at age 73 years obtained from running the 10,000 posterior sample runs.

Figure 6.5-2: Distribution of "Difference in Number of Survivors at Age 73" Between the Single-Cohort Master and Base Case Scenarios



Note: n = 10,000 modeling runs.

6.5.7.4. Sensitivity Analysis #1: Varying Individual Transitions to Understand the Contribution of Each Individual Transition to the Observed Net Benefit

To understand the contribution of each individual transition to the overall net benefit observed (i.e., 1,120 additional survivors at age 73 for the 1,000,000 male cohort, followed from age 13), Table 6.5-4 and Table 6.5-5 display results from seven simulations. These seven Modified Case scenarios were constructed by varying one of the key individual transitions of interest at a time, while keeping all other transitions the same as those in the Base Case.

With the point estimates and associated uncertainty analysis, we identified the parameters that have the greatest impact on the model's results. As a starting point for the uncertainty analysis, a point estimate was generated, representing the impact to the population if that transition was the only transition to impact the population.

Table 6.5-4: Individual Transitions for Modified Cases Based on the ALCS CCI Study Inputs: Point Estimates and 95% Credible Intervals

Transitions	Percent Change in Transition Rates between Base Case and Modified Case	Model Estimate of Difference in Survivors (Modified Case – Base Case) at Age 73 y	Credible Interval for Modeling Estimates
Never-tobacco → MRTP	-5%	10	(-14, 36)
FMST → MRTP	0%	0	-
CIG → MRTP	+21%	425	(366, 489)
CIG → DUAL (MRTP + CIG)	+24%	282	(210, 363)
DUAL (MST + CIG) →MRTP	+6%	69	(60, 76)

ALCS = Altria Client Services LLC; CIG = cigarette smoker; DUAL = current cigarette smoker and current MRTP or MST user; FMST = Former MST User; MRTP = candidate product is authorized as a Modified Risk Tobacco Product; MST = Moist Smokeless Tobacco

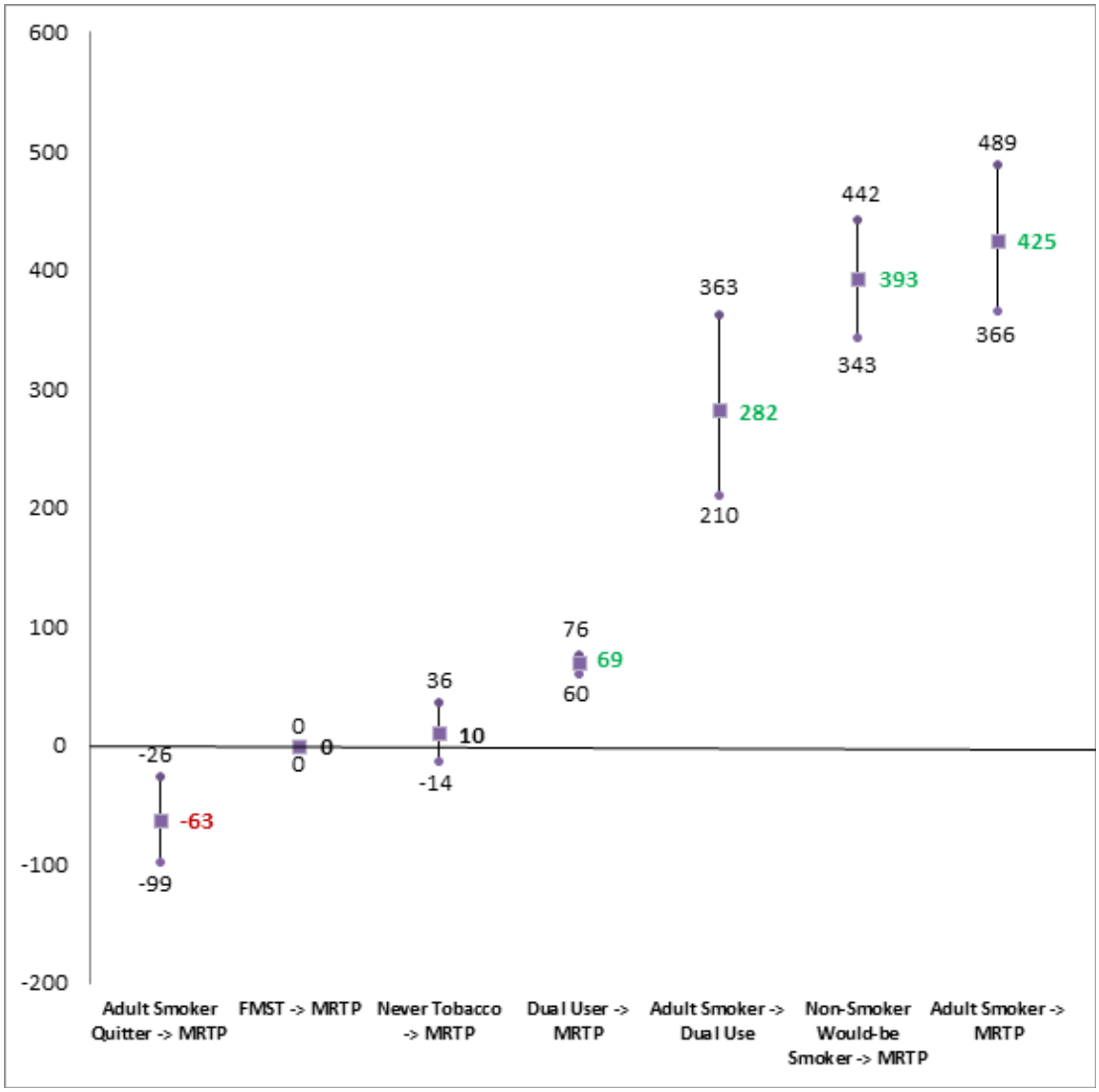
Table 6.5-5: Individual Transitions that Cannot be Estimated from the ALCS CCI Study for Modified Cases: Point Estimates and 95% Credible Intervals

Transitions	Absolute Percent Increase between Base Case and Modified Case[1]	Model Estimate of Difference in Survivors (Modified Case – Base Case) at Age 73 y	Credible Interval for Modeling Estimates
Would-be Smoker → MRTP[2]	+1%	393	(343, 442)
Would-be Smoking Quitter → MRTP	+5%	–63	(–99, –26)

[1] These two subpopulations do not exist in the Base Case; hence, the percentages increase from zeros in the base case to the percentages reported in the table.
[2] MRTP = candidate product is authorized as a Modified Risk Tobacco Product

As seen in Figure 6.5-3, sorting the individual point estimates in order of ascending benefit (i.e., increasing number of additional survivors between Modified Case and Base Case) allows us to understand the contribution of varying transitions related to individual populations of interest described within the MRTPA Draft Guidance, to the overall net benefit, observed between the Master Case and Base Case scenarios.

Figure 6.5-3: Mean Difference in Number of Survivors Between the Master and Base Case Scenarios: Point Estimates and Credible Intervals



Dual User = current cigarette smoker and current MRTP tobacco user; FMST = former moist smokeless tobacco user; MRTP = intended to reflect MST use.

As shown in Figure 6.5-3, the largest detrimental impact (below the baseline) comes from cigarette smokers who were intending to quit but decided to use the MRTP instead (63 fewer survivors). The greatest benefits are realized (far right of Figure 6.5-3) by moving members from higher relative risk states, such as exclusive cigarette smoking and dual use, to lower relative risk states, such as exclusive MST use, and by intercepting adults who would have otherwise started smoking, in absence of a MST product with authorization to be marketed with a modified risk claim, on the market. As seen in Figure 6.5-3, under the conditions employed for scenario analysis with the model, the highest positive impact (425 additional survivors) arose from cigarette smokers switching to exclusive MST use. The benefits of

intercepting smoking initiators and transitioning them to initiating MST use instead (393 additional survivors) and transitioning exclusive cigarette smokers to dual use (282 additional survivors) are of comparable magnitudes.

The next highest contribution to the net benefit comes from varying the dual users to exclusive use transition (69 additional survivors). As previously indicated, this transition rate may increase by 6% with the authorization of the proposed claim (Table 6.5-4). Although dual use and cigarette smoking states have comparable relative risks in the model, the benefit is probably realized due to changes in transition behavior. As indicated by the transition rates summarized from Tam et al. (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 four-year adult transition rate from dual use to exclusive MST use is 17.4 percent, as opposed to the four-year adult transition rate from exclusive smoking to exclusive MST use, which is 1.4 percent.

As seen in Figure 6.5-3, the relatively small changes in transition rates between the Base Case and the Modified Cases for both (1) former MST users switching to MST and (2) never tobacco users initiating with MST have minimal impact on the net benefit estimates (i.e., 0 and 10 deaths prevented, respectively).

6.5.7.5. Sensitivity Analysis #2: Understanding How Potential Variations in Input Parameters Could Influence Modeling Outcomes

The ALCS Cohort Model uses multiple input parameters, each with uncertainty. Understanding how potential variations in input parameters could influence the model outcomes is important for understanding and interpreting its results. We conducted a sensitivity analysis by systematically varying a given parameter around its estimated value to assess its effect on the overall model, holding all other values constant.

For the transition probability changes estimated from the ALCS CCI Study (Appendix 7.3.2-1), we varied the percent change estimates. The breadth of the sensitivity analysis ranged from 0 (i.e., no change between the pre-test and post-test populations) to two times (i.e., two-fold increase from the actual percentage change between the pre-test and post-test populations used in the Master Case scenario). For example, consider the first row in Table 6.5-6. The point estimate value for the percent change between test and control group in the ALCS CCI Study was -5% for this transition. In this case, we varied its value from 0% to -10%, with -10% being the 2X value of the point estimate of -5%. The corresponding results are shown in the third column of Table 6.5-6. Likewise, we varied each transition from 0 to its corresponding two-fold increase value. Due to the hypothetical nature of these scenarios, the two subpopulations that could not be assessed in the ALCS CCI Study are: (1) “Would-be Cigarette Smokers,” those initiating the candidate product instead of smoking; and (2) “Would-be Smoking Quitters,” those initiating the candidate product instead of completely quitting all tobacco use. For these populations, the sensitivity analyses assumed a range of potential transition probabilities.

Table 6.5-6 and Table 6.5-7 summarize the sensitivity analysis results obtained by varying the seven individual transition rates and provide the low and high estimates from the

sensitivity analysis. The ALCS CCI Study did not measure likelihood transition rates to cigarette smoking from exclusive of MST or dual use of MST and cigarettes. For analysis and modeling purposes, we assume that the Base Case transition rates of switching to cigarettes from exclusive MST or dual use established in the literature (Tomar, 2003; Wetter et al., 2002; Zhu et al., 2009) will not change with authorization of the proposed claim.

The modeling results presented as point estimates in the tables below are the same as the ones in Table 6.5-4 and Table 6.5-5 and are discussed in detail in Section 7.4.2.3.4.

Table 6.5-6: Sensitivity Analysis: Mean Difference in Number of Survivors Between Modified Cases based on ALCS CCI Study Inputs and Base Case at 73 Years

Transitions	Percentage Change Point Estimate (Percentage Change Range)	Mean Difference in Number of Survivors between Modified Case and Base Case at Age 73 y Point Estimate (Outcome Range based on Percentage Change Range)
Never-tobacco → MRTP	-5% (-10%-0%)	10 (0, 21)
FMST → MRTP	0%	-
CIG → MRTP	21% (0%-42%)	425 (0, 844)
CIG → DUAL (MRTP + CIG)	24% (0%-48%)	282 (0, 556)
DUAL (MST + CIG) →MRTP	6% (0%-12%)	68 (0,135)

CIG = cigarette; FMST = Former MST User; MRTP = candidate product is authorized as a Modified Risk Tobacco Product; MST = Moist Smokeless Tobacco

Table 6.5-7: Sensitivity Analysis: Mean Difference in Number of Survivors Between Modified Cases that Cannot Be Estimated from the ALCS CCI Study and Base Case at Age 73 Years

Transitions	Absolute Percentage Increase between Base Case and Modified Case[1] (Absolute Percentage Increase Range)	Mean Difference in Number of Survivors between Modified Case and Base Case at Age 73 Point Estimate (Outcome Range based on Absolute Percentage Increase Range)
Would-be Smoker → MRTP[2]	1% (0% - 5%)	393 (0, 1963)
Would-be Smoking Quitter → MRTP	5% (0% - 10%)	-63 (-126, 0)

MRTP = candidate product is authorized as a Modified Risk Tobacco Product; MST = Moist Smokeless Tobacco
[1] These two subpopulations do not exist in the base case so the percentages increase from zeros in the base case to the percentages reported in the table.

6.5.7.6. Results from Multi-Cohort Analysis

As previously discussed in Section 6.5.5.2, we implemented and validated a multi-cohort approach to extend our results from the single-cohort model to the U.S. native-born male population, due to the higher prevalence of MST use among males and extremely low prevalence among females. The multiple-cohort modeling approach employs a single-cohort model in a multiple-cohort setting, with a time-staggered structure.

This modeling analysis was implemented both in the Base Case and Master Case scenarios, where it was assumed that authorization of the proposed claim was issued in the year 2015. In this analysis, for the Modified Case, we use the same parameters as those used in the Master Case scenario described in Section 6.5.6.4. Under the scenario in which the MRTP is introduced in 2015, we followed multiple cohorts until the year 2075 under the Base Case (i.e., the status quo), and Master Case (i.e., the most likely scenario that would result from authorization of the proposed claim) scenarios. By comparing the difference in the number of living persons in all age categories between these scenarios in the year 2075, we can make inferences about the impact of authorizing the modified risk claim. Table 6.5-8 shows the results of the Master Case and Base Case scenarios across age groups for the year 2075 and the difference in the number of survivors between the two scenarios for males alive from ages 0 to 84 years.

Table 6.5-8 shows that the total number of living persons across all age groups in the Master Case scenario increases by 93,323 by the year 2075, when compared with the Base Case scenario. The difference in the number of living persons in the Master Case versus the Base Case scenario increases rapidly from ages 40 to 74 years, before beginning to slightly decline. This trend aligns with the observation and explanation by Rostron (2011) that mortality ratios associated with smoking in males increase with age from 45 to 74 years, before slightly declining at older ages.

Table 6.5-8: The Expected Difference in the Year 2075 Between the Master and Base Case Scenarios in the Number of People Alive by Age Groups

Age Group (years)	Master Case	Base Case	Difference
0-4	11,659,500	11,659,500	0
5-9	11,503,227	11,503,227	0
10-14	11,343,808	11,343,808	0
15-19	11,384,863	11,384,863	0
20-24	11,210,354	11,210,354	0
25-29	10,975,495	10,975,342	153
30-34	10,691,665	10,691,192	473
35-39	10,398,367	10,397,394	973

Age Group (years)	Master Case	Base Case	Difference
40-44	10,101,332	10,099,412	1,920
45-49	9,787,295	9,783,564	3,731
50-54	9,355,425	9,348,637	6,788
55-59	8,757,301	8,747,530	9,771
60-64	8,050,922	8,038,615	12,307
65-69	7,691,177	7,676,364	14,813
70-74	6,889,508	6,873,894	15,614
75-79	5,774,009	5,759,539	14,470
80-84	4,761,915	4,749,605	12,310
Total Additional People Alive in the Master vs. Base Case			**93,323**

Importantly, the multiple-cohort modeling exercise allows us to extend the prediction of an additional 1,120 survivors from a 1,000,000 male cohort in the single-cohort approach to a larger U.S. native-born male population. Under the defined modeling scenarios, we predict authorization of the proposed claim will result in approximately 93,000 more people being alive at the end of a 60-year follow-up period, compared with the status quo.

Finally, the current market share for Copenhagen® Snuff Fine Cut allows us to scale the results of the multi-cohort approach to more realistically estimate the net benefit to the U.S. native-born male population, if an MRTP claim is authorized for the candidate product. The current U.S. market share is approximately 8%;[2] therefore, 7,500 of the 93,000 additional lives resulting from the multiple cohort modeling approach represents the net benefit of our candidate product. We have made a conservative assumption that the market share of the candidate product would remain the same for 60 years, after the candidate product receives authorization to be marketed with the proposed claim. Though it is quite reasonable to expect that if the proposed claim is authorized, as users begin to better understand the lower health risks of switching completely to the candidate product from cigarette smoking, additional users may switch from exclusive smoking and/or dual use to exclusive use of the candidate product, thereby further increasing this projected net benefit.

6.5.8. Conclusions

Our model comparing the Master Case and Base Case scenarios indicates that authorization of the proposed modified risk claim for the candidate product yields a net population health benefit. These findings come from a validated model that was developed using a published list of modeling best practices and tested using uncertainty and sensitivity analyses.

[2] Source: IRI Info Scan Smokeless 2017-MOC, for year ending 12/31/17

The model results showed that for a single cohort of 1,000,000 males, the most likely outcome of authorization of the proposed claim yielded 1,120 additional survivors with 32,856 additional years of expected life, when compared with the status quo. We used a multiple-cohort modeling approach to extend the modeling predictions to the U.S. native-born male population. Results suggest that authorization of the proposed claim would lead to an increase of approximately 93,000 more people being alive over a follow-up period of 60 years, as compared with the status quo (i.e. Base Case). Moreover, when factoring the market share of the candidate product from the category-level estimates, the expected net benefit to the U.S. native-born male population is that an additional 7,500 people will be alive after a follow-up period of 60 years, when compared with the status quo.

6.5.9. Literature Cited

Accortt, N. A., Waterbor, J. W., Beall, C., & Howard, G. (2002). Chronic disease mortality in a cohort of smokeless tobacco users. *American journal of epidemiology, 156*(8), 730-737.

Arias, E. (2010) United States life tables, 2006. *National vital statistics reports: Vol. 58*: National Center for Health Statistics.

Bachand, A. M., & Sulsky, S. I. (2013). A dynamic population model for estimating all-cause mortality due to lifetime exposure history. *Regulatory Toxicology and Pharmacology, 67*(2), 246-251.

Bachand, A. M., Sulsky, S. I., & Curtin, G. M. (2017). Assessing the Likelihood and Magnitude of a Population Health Benefit Following the Market Introduction of a Modified-Risk Tobacco Product: Enhancements to the Dynamic Population Modeler, DPM(+1). *Risk Analysis*. doi:10.1111/risa.12819

Boone, R. J., Muhammad-Kah, R. S., Pithawalla, Y. B., Wei, L., Frost-Pineda, K., & Gogova, M. (2016). *Combining Statistical and Compartmental Models for Use in Tobacco Product Risk Assessments*. Paper presented at the Conference on Statistical Practice, San Diego.

Caro, J. J., Briggs, A. H., Siebert, U., & Kuntz, K. M. (2012). Modeling good research practices--overview: A report of the ISPOR-SMDM modeling good research practices task force-1. *Medical Decision Making, 32*(5), 667-677.

Cherng, S. T., Tam, J., Christine, P. J., & Meza, R. (2016). Modeling the Effects of E-cigarettes on Smoking Behavior: Implications for Future Adult Smoking Prevalence. *Epidemiology, 27*(6), 819-826. doi:10.1097/ede.0000000000000497

Friedman, G. D., Tekawa, I., Sadler, M., & Sidney, S. (1997). Smoking and mortality: the Kaiser Permanente experience. In D. M. Burns, L. Garfinkel, & J. M. Samet (Eds.), *Changes in cigarette-related disease risks and their implications for prevention and control* (pp. 477-499). Rockville, MD: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

Frost-Pineda, K., Appleton, S., Fisher, M., Fox, K., & Gaworski, C. L. (2010). Does dual use jeopardize the potential role of smokeless tobacco in harm reduction? *Nicotine & tobacco research, 12*(11), 1055-1067.

Hill, A., & Camacho, O. M. (2016). *A Systems Dynamic Approach for Assessing Potential Health Impacts as Result of Launching a Nicotine Product in a Market*. Paper presented at the Society for Research on Nicotine and Tobacco Annual Meeting, Chicago, IL.

Hill, A., & Camacho, O. M. (2017). A system dynamics modelling approach to assess the impact of launching a new nicotine product on population health outcomes. *Regulatory Toxicology and Pharmacology, 86*(Supplement C), 265-278. doi:https://doi.org/10.1016/j.yrtph.2017.03.012

Lee, P. N., Fry, J. S., Hamling, J. F., Sponsiello-Wang, Z., Baker, G., & Weitkunat, R. (2017). Estimating the effect of differing assumptions on the population health impact of introducing a Reduced Risk Tobacco Product in the USA. *Regul ToxRegulatory Toxicology and Pharmacology, 88*, 192-213. doi:10.1016/j.yrtph.2017.06.009

Levy, D. T., Borland, R., Villanti, A. C., Niaura, R., Yuan, Z., Zhang, Y., . . . Abrams, D. B. (2016). The Application of a Decision-Theoretic Model to Estimate the Public Health Impact of Vaporized Nicotine Product Initiation in the United States. *Nicotine & tobacco research*. doi:10.1093/ntr/ntw158

Poland, B., & Teischinger, F. (2017). Population Modeling of Modified Risk Tobacco Products Accounting for Smoking Reduction and Gradual Transitions of Relative Risk. *Nicotine &Tobacco Research, 19*(11), 1277-1283. doi:10.1093/ntr/ntx070

Rostron, B. (2011). Smoking-attributable mortality in the United States. *Epidemiology, 22*(3), 350-355.

Tam, J., Day, H. R., Rostron, B. L., & Apelberg, B. J. (2015). A systematic review of transitions between cigarette and smokeless tobacco product use in the United States. *BMC public health, 15*, 258. doi:10.1186/s12889-015-1594-8

Tomar, S. L. (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., Alpert, H. R., & Connolly, G. N. (2010). Patterns of dual use of cigarettes and smokeless tobacco among US males: findings from national surveys. *Tobacco control, 19*(2), 104-109.

United States Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse. Food and Drug Administration. Center for Tobacco Products. (2017). *Population Assessment of Tobacco and Health (PATH) Study [United States] Public-Use Files*. Retrieved from: http://doi.org/10.3886/ICPSR36498.v6

United States Department of Health and Human Services. Substance Abuse and Mental Health Services Administration. Center for Behavioral Health Statistics and Quality. (2016). *National Survey on Drug Use and Health, 2014*. Retrieved from: http://doi.org/10.3886/ICPSR36361.v1

Vugrin, E. D., Rostron, B. L., Verzi, S. J., Brodsky, N. S., Brown, T. J., Choiniere, C. J., . . . Apelberg, B. J. (2015). Modeling the potential effects of new tobacco products and policies: a dynamic population model for multiple product use and harm. *PloS one, 10*(3), e0121008.

Weitkunat, R., Lee, P. N., Baker, G., Sponsiello-Wang, Z., Ladd, A. M. G., & L++dicke, F. (2015). A novel approach to assess the population health impact of introducing a Modified Risk Tobacco Product. *Regulatory Toxicology and Pharmacology, 72*(1), 87-93.

Wetter, D. W., McClure, J. B., de Moor, C., Cofta-Gunn, L., Cummings, S., Cinciripini, P. M., & Gritz, E. R. (2002). Concomitant use of cigarettes and smokeless tobacco: prevalence, correlates, and predictors of tobacco cessation. *Preventive medicine, 34*(6), 638-648.

Zhu, S.-H., Wang, J. B., Hartman, A., Zhuang, Y., Gamst, A., Gibson, J. T., . . . Galanti, M. R. (2009). Quitting cigarettes completely or switching to smokeless tobacco: Do U.S. data replicate the Swedish results? *Tobacco control, 18*(2), 82-87.