6.4 Statistical Modeling of the Effects on the Health of the Population as a Whole

Under Section 911(g)(1) of TCA, the granting of an MRTP order is based on the expected effects of the order on the health of the population as a whole. Accordingly, a tobacco product proposed for an MRTP order must meet two criteria.

First, FDA must determine that the tobacco product, as actually used by consumers, will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" (TCA Section 911(g)(1)(A); FDA MRTPA Draft Guidance 2012, p. 3). Accordingly, throughout this Application, RJRT presents a wide body of scientific studies and data applicable to Camel Snus (product design and composition, comparative harmful and potentially harmful constituents (HPHC) chemistry, comparative preclinical toxicology, epidemiology, and human clinical studies) that demonstrate that use of Camel Snus is associated with much less risk than smoking. Indeed, a panel of experts (Levy *et al*. 2004) estimated that snus was associated with 89% to 92% less mortality risk than smoking.

Second, FDA must determine that the broader impact of a proposed MRTP "benefit[s] 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users of tobacco products and persons who do not currently use tobacco products" (TCA Section 911(g)(1)(B); FDA MRTPA Draft Guidance 2012, p. 3). As described Section 6.3, RJRT collected data from both users and non-users of tobacco products in order to estimate their likelihood of using Camel Snus with the proposed modified risk advertising. These data, in turn, inform the expected effect of the MRTP and its proposed modified risk advertising on population health. That is, the impact of an MRTP on population health depends on its effect on the health of individuals using and not using various tobacco products and also on population changes in tobacco product use that may result from the introduction of the MRTP and its associated modified risk advertising.

The expected effect of an MRTP order on population health must be assessed in a pre-market context, before the MRTP and associated modified risk advertising are disseminated. Thus, the effects cannot directly be observed at the time an MRTP order is granted. Accordingly, the expected effects of the MRTP on population health must be estimated through statistical modeling, taking into account likely changes in population tobacco use behavior, and their resulting effects on health. Statistical modeling of the impact of the availability of an MRTP and its proposed modified risk advertising on population health is likely to produce reliable and accurate predictions if the model is well-validated, and the inputs to the model – including changes in likely tobacco use behaviors and their effects on individual health as compared to the status quo – are rooted in empirical evidence. This section presents the results of an empirically-informed statistical modeling exercise, showing that an MRTP order for Camel Snus with the proposed modified risk advertising is likely to produce a net benefit for population health.

6.4.1 Statistical Modeling and the Dynamic Population Modeler (+1)

Statistical modeling has been widely used to support regulatory decision-making in a variety of contexts, from housing and transportation, to the impact of health risk factors such as obesity and substance abuse (*e.g.*, National Academies of Sciences, Engineering, and Medicine 2016). Specifically applied to tobacco health policy, six statistical models have been designed to estimate the population health effects of introducing an MRTP to a population (Apelberg *et al*. 2010; Levy *et al*. 2004; Mejia *et al.* 2010; Poland and Teischinger 2016; Vugrin *et al*. 2015; Weitkunat *et al*. 2015). These models have been able to evaluate the impact of a variety of tobacco use behaviors and their associated risks on health outcomes, such as morbidity and disability. However, there are important differences among the models that affect their ability to estimate accurately the impact of the availability of various tobacco products on population health. For example, the Apelberg *et al*. 2010 and Mejia *et al*. 2010 models are limited by the range of questions they can address because they do not allow smoking initiation and cessation rates to depend on age and incorporate only a very limited number of transitions between tobacco exposure states. The Poland and Teischinger 2016, Vugrin *et al*. 2015, and Weitkunat *et al*. 2015 models follow a cross-section of the population over time. However, this approach can also result in conceptual inconsistencies that lead to invalid results (see below). The preferred statistical modeling approach follows a birth cohort over time to assess the likely effects of changes in tobacco use patterns or exposures on net population health.

The Dynamic Population Modeler (DPM) (+1) (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report) is a fit-for-purpose statistical model designed to meet the modeling specifications outlined in the MRTPA Draft Guidance (FDA MRTPA Draft Guidance 2012). As is outlined in detail below, the DPM(+1) has been found to accurately predict life tables for large populations over time using age and tobacco use as the only risk factors (Bachand and Sulsky 2013). It estimates the impact of an MRTP and its proposed modified risk advertising on population health by comparing a base case (cigarette smoking, with its attendant effects on population health) to a counterfactual scenario (*i.e.*, hypothetical alternative exposure involving access to Camel Snus with modified risk advertising as well as cigarettes). The DPM(+1) then calculates a population health impact by projecting differences in the number of survivors between the base case and the counterfactual scenario.

The DPM(+1) starts with a hypothetical population cohort of 1 million males with no tobacco exposure at age 13[1] and, following that cohort as it ages, it distributes subsets of the cohort

[1] This cohort size and single-gender approach was chosen for convenience. The actual population of a single-year's birth cohort in the U.S. is slightly more than four million, and is a mix of males and females. The survival estimates

into exposure categories (*e.g.*, non-user of tobacco, cigarette smoker, Camel Snus user, etc.), and applies an estimated mortality rate to each exposure category. The model contrasts two scenarios: (1) a base case in which the population may smoke (but not use Camel Snus or any other tobacco product), and (2) a counterfactual scenario in which some in the population may instead use Camel Snus as a modified risk tobacco product. In this manner, the DPM(+1) estimates the effects on all-cause mortality in the population to address the likely effects on population health resulting from the granting of an MRTP order for Camel Snus.

The key benefit of using modelers like the DPM(+1) to estimate the effects of public health policies aimed at shifting populations from more harmful to less harmful tobacco exposures is their ability to hold constant all assumptions and factors other than the distribution of tobacco exposures and their comparative risk estimates (Bachand and Sulsky 2013). The DPM(+1) estimates the population health effects of Camel Snus by modeling transitions among three tobacco use states in the population (*e.g.*, no tobacco use, cigarette smoking, use of Camel Snus). For the present modeling, dual use (*i.e.*, cigarette smoking plus use of Camel Snus) is treated as smoking from a health impact perspective. Transition probabilities are then used to estimate the likely exposure patterns to be compared in the base case where only cigarettes are available for use and counterfactual scenarios where cigarettes and Camel Snus are available for use. The assumed, or when possible empirically-estimated, probabilities of each transition are explicit inputs that can be varied, and the modeler includes age-specific changes, or transitions, in tobacco use that are specified to occur across a variety of age intervals throughout the duration of follow-up.

In the base case, never tobacco users can remain never users or they can begin cigarette smoking; and cigarette smokers can continue to smoke or they can quit. The modeler permits transitions every 5 years, starting at age 13. Smoking initiation and cessation probabilities used in the DPM(+1) are derived from empirical estimates based on actual values from the U.S. population. The respective probabilities are entered as either fixed probabilities or as probabilities with some degree of uncertainty (as random probabilities from a normal distribution, truncated at 0 and 1, with the point estimate of the probability as the mean and an analyst-specified variance). Mortality was calculated for each age interval of follow-up by a Poisson model, which defines mortality relative risks by age, duration of exposure, and, for those who quit, duration of cessation, among current and former cigarette smokers compared to never smokers. Survivors of each age interval move to the next age interval, where they can remain in their current tobacco use category or transition to a different tobacco use category. The modeler estimates the number of survivors remaining in the population in each age interval. Survival to age 72 is the key output of the model; at later ages, survival trends towards 0, and differences between smokers and non-smokers narrow, making those data less informative.

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initially reported are based on the 1 million-male cohort, but a subsequent table scales them to the true size of a single birth cohort and adjusts for the mixed-gender population.

6.4.1.1 Overview of Analyses for Camel Snus MRTP

The counterfactual scenarios assessed by the DPM(+1) assume that Camel Snus, with modified risk advertising, is available for the population to use. Mortality risks for those smokers who switch to Camel Snus are reduced based on the estimated excess relative risk (ERR), comparing the use of Camel Snus to cigarette smoking. The ERRs compare excess mortality among current and former Camel Snus users to current and former cigarette smokers, respectively. As in the base case, survivors at the end of each age interval move to the next age interval, during which time they can remain in their current tobacco use category or transition to a different tobacco use category. The proportion of the population transitioning between other tobacco use categories and Camel Snus use is explicitly posited, based on empirical estimates from the likelihood of use study or on other values of conceptual interest, such as extreme values (*i.e.*, to test the limits or tipping points in the model output where population health effects shift from positive to negative, or vice versa).

The net effect of a Camel Snus MRTP and its proposed modified risk advertising on population health is estimated by the DPM(+1) by calculating the number of survivors remaining in the cohort at ages 68-72 in the counterfactual scenario (*i.e.*, including both smoking and the availability of Camel Snus) and comparing it to the number of survivors in the base case (*i.e.*, cigarette use only). Because the DPM(+1) model inputs are subject to uncertainty, the modeled predictions are expressed as a range of outcomes with various probabilities. The coefficients of the Poisson model that are used to define mortality risks are estimated using a Bayesian approach and Markov Chain Monte Carlo techniques. Ten thousand sets of model coefficients are generated after a burn-in of 2,000 iterations. Uncertainty in initiation and cessation probabilities is accounted for by modeling the transition probabilities as truncated normal random variables, with means equal to the respective estimates and standard deviations equal to 0.01. The ERRs are also entered as numeric values with some degree of uncertainty. A range of ERR values is generated using a left-truncated normal distribution, with the point estimate of the ERR as the mean and a hypothesized variance. For the base case and counterfactual scenario, survivors are estimated for each set of Poisson model coefficients and initiation and cessation probabilities (*i.e.*, for each iteration), and means with 95% posterior intervals (95% PI) are reported. The PI represents the range within which the net effect is likely to fall (with 95% certainty), given the posited uncertainties in the model inputs. Thus, the DPM(+1) can help to inform regulatory decision-making by estimating the likely net population health effect, under a variety of empirically-based model inputs, of a Camel Snus MRTP being available with modified risk advertising.

6.4.1.2 Simplifying assumptions incorporated into analyses for Camel Snus MRTP

Like all modelers, the DPM(+1) makes some simplifying assumptions to help make tractable the challenge of quantifying and estimating the long-term, real-world impact of an MRTP's availability. It assumes that the health effects of tobacco use vary entirely with tobacco use status (smoking or not, using Camel Snus or not) and duration, but do not vary with the amount of smoking or quantity of Camel Snus used. The DPM(+1) considers dual use of Camel Snus

along with smoking to have the same mortality risk as smoking; thus, it is not included in the model inputs as a separate tobacco use category but is assessed as smoking. The DPM(+1) does not incorporate any effects of smoking or Camel Snus use on the health of others who may be exposed to environmental tobacco smoke (when the individual in question is smoking) or spared such exposure (when the individual is using Camel Snus). As is necessary in modeling a hypothetical future scenario, the analyses assume that past or present data are applicable to the future experience of the cohort being modeled. A simplifying assumption for these analyses is that in the base case only smoking is considered, and not multiple products that are currently available in the U.S. (*e.g.*, other combustibles, smokeless tobacco products, and electronic nicotine delivery devices). Similarly, the counterfactual scenario adds the availability of Camel Snus and does not consider the simultaneous availability of other tobacco products[2]. Although the current analyses explicitly provide for cessation of smoking (*i.e.*, transitions from smoking to abstinence), with a consequent reduction in risk for those individuals, they do not allow for abstinent individuals to relapse back to smoking; quitting is modeled as a persistent state.

The analyses conducted also did not provide for a transition from Camel Snus to tobacco abstinence (individuals who adopt Camel Snus can transition to smoking, but not to abstinence) because data on the rate of quitting Camel Snus are not available.

As stated above, the DPM(+1) estimates transitions over time in tobacco use of a single cohort of individuals who start out with no tobacco use at age 13. The DPM(+1) applied to a single cohort does not take into account the effects of a Camel Snus MRTP order on the full population, which includes older cohorts and adults who are already smoking when the MRTP order goes into effect. In other words, the DPM(+1) does not estimate the potential health benefits and risks of having Camel Snus available for current smokers; thus, modeling of a single, tobacco naïve cohort underestimates the potential health benefit of Camel Snus MRTP availability. Component analyses present a heuristic model that additionally considers the likely health effects on the full population, rather than just a single cohort modeled over time (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report).

6.4.1.3 Modeling the dynamics and health effects of cigarette smoking in the base case

Estimating the impact of Camel Snus on population health involves assessing how the introduction of MRTP advertising for Camel Snus is likely to change population health, compared to the expected population health absent the modified-risk advertising.

[2] The analyses do not allow for switching from other smokeless tobacco products to snus. To the extent that occurs and presents some decrease in risk, the population benefit would be underestimated.

6.4.1.3.1 Cigarette smoking transitions

To estimate population smoking behavior in the base case, the DPM(+1) uses data from the National Survey on Drug Use and Health (NSDUH) as inputs for smoking initiation and cessation by age (Table 6.4.1-1). Note that smoking initiation is modeled as peaking during ages 13-17, and as being essentially null after age 22. Conversely, smoking cessation is specified as reaching a peak during the age 28-32 age interval and stays at that level for the rest of the cohort's life.

Table 6.4.1-1: Estimated* U.S. smoking initiation (2009) and cessation (2005-2008) rates

Age Interval	Smoking Initiation (%)[a]	Smoking Cessation (%)[b]
13-17	13.75	N/A[c]
18-22	10.00	9.00
23-27	1.00	9.50
28-32	0.00	14.00
33-37	0.00	14.00
38-42	0.00	14.00
43-47	0.00	14.00
48-52	0.00	14.00
53-57	0.00	14.00
58+	0.00	14.00

*Rates were adjusted to align with the 5-year age intervals used in the DPM(+1) and were multiplied by 2.5 to estimate rates over a 5-year period (*i.e.*, to provide a conservative estimate of the average person-time at risk of smoking initiation or cessation in each 5-year age interval).

[a] http://www.samhsa.gov/data/NSDUH/2K10ResultsTables/NSDUHTables2010R/HTM/Sect4peTabs1to16.htm#Tab4.3B

[b] http://www.samhsa.gov/data/2k10/172/172smokingcessation.htm

[c] No smoking cessation is allowed in the first age interval, 13-17 years, when initiation is first taking place.

6.4.1.3.2 Cigarette smoking mortality

Age-specific mortality rates for current, former, and never smokers were derived from the Kaiser-Permanente Cohort Study data (Friedman *et al*. 1997) and the 2000 U.S. Census, with some adjustments (Bachand and Sulsky 2013). The Kaiser-Permanente data source is uniquely suited for this purpose, as it is the only one available that provides mortality rates by age, gender, duration of smoking, and duration of smoking cessation.

To assess population health effects, it was also necessary to incorporate the residual health risk that smokers may incur even after they have stopped smoking. This residual risk was also estimated from the Kaiser-Permanente dataset.

On the basis of these model inputs, the DPM(+1) estimates how many individuals survive to age 72 or older (*i.e.*, to the end of the age 68-72 5-year age interval). Survival into this age is considered the key indicator of tobacco-related mortality, as the mortality of smokers and non-smokers begins to converge at older ages, and survival rates trend rapidly towards zero. Importantly, the model is based on mortality estimates for males. Analyses based on female

mortality data show a smaller population benefit for a Camel Snus MRTP, but with tipping points that are nearly identical to those for males (see Appendix H in Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report).

The model outputs of the DPM(+1) are also used to estimate life expectancy and quality-adjusted life expectancy[3]. As these outputs depend on the survival calculations, which are the primary end-points of the modeling, this section focuses only on survival.

6.4.1.4 Validating the DPM(+1)

Models can be validated by evaluating their ability to 'predict' a known outcome. Two validation assessments were run for the DPM(+1) (Bachand and Sulsky 2013). One used the DPM(+1) to predict the mortality in the U.S. population, based on the model assumptions about the dynamics of smoking behavior and the impact of smoking on mortality. A second used Swedish data on the use of snus, and transitions between smoking and snus, to predict mortality outcomes in Sweden. As described below, in both assessments the 'predictions' from the DPM(+1) closely match the actual observed experience. Jointly, these two validation assessments, covering the dynamics and health effects of cigarette smoking (the base case) and the health effects of snus (crucial to the counterfactual scenarios), demonstrate the validity of the DPM(+1) and the model's inputs and assumptions to estimate all-cause mortality in a population transitioning from smoking to Camel Snus use. Thus, the DPM(+1) is an appropriate statistical model that can be used to estimate the expected net population health effects of Camel Snus' availability as an MRTP with modified risk advertising.

6.4.1.4.1 Validating the DPM(+1) base case model of smoking

The DPM(+1) base case – considering only smoking – was validated against actual observed population health statistics by generating modeled tobacco use behaviors and comparing the

[3] The quality-of-life adjustments to life expectancy are based on overall age-related changes in quality-of-life and are not specific to the particular effects of smoking-related disease (*e.g.*, COPD has significant adverse effects of quality-of-life), so they do not provide additional smoking-related information. Detailed accounts of the life expectancy and quality-adjusted life expectancy outcomes are available in Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report.

resulting life tables to known population life tables. In effect, the DPM(+1) was used to 'predict' the past, as its model-derived projections of population health effects were compared to actual observed mortality outcomes.

Specifically, the DPM(+1) was used to estimate mortality in 2006 using age-specific 1980 U.S. smoking initiation (Substance Abuse and Mental Health Services Administration 1999) and smoking cessation rates (Messer *et al*. 2007)[4]. The modeled results were compared to the 2006 U.S. life table for men (Arais 2010). Table 6.4.1-2 shows the results – the number of survivors estimated by the DPM(+1) base case was within 0.2% of the U.S. life table-based actual number of survivors. This demonstrates that the estimates derived from the DPM(+1) very closely match the observed mortality experience of the U.S. population, validating the DPM(+1) and its base case assumptions.

Table 6.4.1-2: Age-specific estimated survivors: 2006 U.S. life table versus model-based estimates (starting with 1,000,000 13-year-old male never tobacco users)

Age interval (years)	Survivors based on U.S. life table	Survivors based on base case model estimate (U.S.)
38-42*	957,654	957,100
43-47	940,866	939,200
48-52	915,745	914,300
53-57	880,470	879,800
58-62	832,268	832,000
63-67	764,922	765,600
68-72	674,217	674,300

*Age interval 38-42 is the first age group where all possible tobacco use transitions have occurred.

6.4.1.4.2 Validating the DPM(+1) counterfactual scenario of smoking with Camel Snus availability

To validate the DPM(+1) estimates of the mortality effects of snus availability, which is important to the counterfactual scenario for this MRTPA, the DPM(+1) was used to estimate mortality within the Swedish male population, which has had substantial adoption of snus. The DPM(+1) uses empirically-observed probabilities of transitioning among cigarettes, snus, and dual use in Sweden (Lundqvist *et al*. 2009), with some adjustments (Bachand and Sulsky 2013).

[4] The modeling conducted to estimate the effects of the Camel Snus MRTP uses more recent data (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report).

The modeler assessed survival using the assumption that the mortality risk of snus is 89% less than smoking (*i.e.*, an ERR of 0.11; Levy *et al.* 2004).

Projections of survival from the DPM(+1) are compared to observed survival rates, based on the 2006 Swedish life table for men. As shown in Table 6.4.1-3, the number of survivors estimated by the DPM(+1) is within 0.3% of the Swedish life table-based number of survivors (Bachand and Sulsky 2013). This demonstrates that the DPM(+1) is a valid tool that can be used to estimate the population-based mortality impact of the availability of Camel Snus as an MRTP.

Table 6.4.1-3: Age-specific estimated survivors: 2006 Swedish life table versus model-based estimates (starting with 1,000,000 13-year-old male never tobacco users)

Age interval (years)	Survivors based on Swedish life table	Survivors based on counterfactual scenario estimate (Sweden)
38-42*	980,999	979,274
43-47	972,889	970,010
48-52	959,782	957,276
53-57	936,838	935,677
58-62	902,590	902,104
63-67	846,884	847,362
68-72	764,275	762,582

* Age interval 38-42 is first age group where all possible tobacco use transitions have occurred.

6.4.2 DPM(+1) parameter specification for assessing the population health impact of Camel Snus and MRTP advertising (the counterfactual scenario)

To estimate the effect on the health of the population as a whole, one must assess how much the MRTP reduces mortality compared to smoking and also how the MRTP with modified risk advertising is likely to change the population's tobacco use behavior, including both beneficial changes (*e.g.*, some individuals who smoke instead switch to Camel Snus and reap the benefit of risk reduction) and harmful changes (*e.g.*, some individuals who otherwise would not have used tobacco at all use Camel Snus and incur new health risks). By considering both health benefits and harms, the model outputs can inform the expected net effect of multiple behavior changes on population health as well as provide insight into the likely impact of any one change in tobacco use behavior. This section addresses how each of the model inputs was specified and discusses how the inputs were estimated and included in the DPM(+1) analyses of the Camel Snus MRTP.

6.4.2.1 Relative risk to an individual user of Camel Snus compared to smoking

One important input parameter to the modeling of the impact of a Camel Snus MRTP is the degree of reduction in the risk of death associated with using Camel Snus instead of smoking (*i.e.*, the risk reduction to the individuals who switch from cigarette smoking to exclusive use of Camel Snus). The DPM(+1) analyses presented here use two estimates of the excess relative risk

Camel Snus). The DPM(+1) analyses presented here use two estimates of the excess relative risk (ERR) of use Camel Snus compared to smoking combustible cigarettes. The estimates are derived from a published consensus estimate for the mortality risk associated with long-term use of a low-nitrosamine smokeless tobacco product relative to smoking conventional cigarettes and no tobacco use (Levy *et al*. 2004). The experts (Levy *et al*. 2004) estimated the relative all-cause mortality risk to be 11% for those aged 35-49 and 8% for those aged 50 or older. The DPM(+1) model was run using each of these two estimates, applied across the entire range of age intervals (*i.e.*, the model was evaluated twice, once with the ERR of using Camel Snus relative to smoking estimated to be 0.08 and again with the ERR estimated to be 0.11). In other words, the mortality risk associated with using Camel Snus is estimated to be either 92% or 89% less than that of smoking.

In the DPM(+1) modeler, uncertainty in the value of the ERR is accounted for by inputting the ERR as a left-truncated normal random variable with a mean equal to the consensus estimate (*i.e.*, 0.08 or 0.11) and a standard deviation of 0.01. Thus, for an ERR of 0.08, the standard deviation ensured an ERR range of approximately 0.05 to 0.11; for an ERR of 0.11, the standard deviation ensured an ERR range of approximately 0.08 to 0.14. Incorporating uncertainty in the exact ERR further strengthens the conclusions regarding the estimated population health impact of MRTP availability. Further, sensitivity analyses were conducted to estimate a tipping point for the posited ERR; that is, to ascertain how high the ERR could be to still result in a benefit from a Camel Snus MRTP within the context of empirically-derived estimates for primary beneficial and harmful transitions, and generally conservative (in most instances, extreme) scenarios for secondary harmful transitions.

The model estimates do not consider that users of Camel Snus may stop using it, or credit any health benefit for such cessation, because there are no data to estimate the likelihood of cessation. It was also necessary to consider the effect of dual use of cigarettes and Camel Snus. Although studies suggest that dual use is associated with a reduction in cigarette consumption (Lund and Lund 2014; Lund and McNeill 2013), the DPM(+1) conservatively assumes that dual use carries the same risk as smoking.

6.4.2.2 Approaches to modeling tobacco use behaviors in a population over time

6.4.2.2.1 DPM(+1) modeling inputs

The DPM(+1) estimates of the impact on population mortality of Camel Snus being available with an MRTP order was assessed using two different approaches. First, empirically-derived estimates of transitions in tobacco use behaviors are based on results from the likelihood of use studies performed to assess consumers' response to each of three proposed MRTP advertising executions (Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *First Execution of Consumer Testing* – Amended Final Report; Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Second Execution of Consumer Testing* – Amended Final Report; Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Third Execution of Consumer Testing* – Amended Final Report). The second approach aims to determine the "tipping points" focusing

on the proportion of continuing smokers who switch to Camel Snus as a key parameter. That is, the tipping point analyses either use empirically-derived estimates or extreme values for harmful tobacco use transitions, and estimate what proportion of smokers would have to switch persistently to Camel Snus in each 5-year age interval in order to counteract the adverse effects of these harmful transitions, to render the resulting net population effect neutral or beneficial[5].

6.4.2.2.1.1 Using empirically-derived inputs of primary tobacco use transitions from the likelihood of use studies

The primary set of DPM(+1) inputs are data collected in RJRT's likelihood of use studies to estimate the probability of key tobacco use transitions. Note that these estimates are specific to each of the three proposed modified risk advertising executions presented in this MRTPA, as assessed in the respective likelihood of use study (Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *First Execution of Consumer Testing* – Amended Final Report; Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Second Execution of Consumer Testing* – Amended Final Report; Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Third Execution of Consumer Testing* – Amended Final Report). With these empirically-based estimates as inputs, the model calculates the projected difference in survival between the base case (smoking and no Camel Snus) and the counterfactual scenario with an MRTP and its proposed modified risk advertising available to the population.

Not all of the required DPM(+1) inputs can be derived empirically from the likelihood of use studies. In particular, secondary tobacco use transitions, in which individuals make one transition to use Camel Snus followed by a second transition (*e.g.*, going from a never-user of tobacco to using Camel Snus and then going on to smoke), cannot be estimated from the likelihood of use data for two reasons. First, it requires respondents to speculate about two sequential hypotheticals (*e.g.*, first to estimate their likelihood of adopting Camel Snus, and then, without even having actually tried Camel Snus, to estimate the likelihood of another transition to smoking). Second, while respondents did provide estimates of the likelihood of this secondary transition, there was no validated model for converting these likelihood ratings into

[5] Although the tipping point is calculated as the probability of persistent *Switching* in each age interval, it is important to recognize that the total, cumulative amount of *Switching* cannot be calculated simply by multiplying the figure by the number of age intervals. The number of 'switchers' at the end of age interval 68-72 years is not only affected by the probability of *Switching* but also by smoking initiation, cessation and deaths, which themselves differ according to the inputs for each analysis. A rough insight into the cumulative effect of *Switching* on the birth cohort is provided by examining the reduction in the number of smokers at the end of age interval 68-72 years as a result of *Switching* (see Appendix G, Table G1 in Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report).

projected probabilities of the actual tobacco use transition. Accordingly, for these secondary tobacco use transitions, values regarded as conservative are used as model inputs. Specifically, each of these secondary tobacco use transitions is input as a 50% probability of occurring.

The tobacco use transition probabilities derived from the likelihood of use studies are not perfect indicators of population behavior. Instead, they are based on survey respondents' rated likelihood to try Camel Snus after having seen a proposed modified risk advertisement. As such, they represent respondents' reactions to a hypothetical proposition, after a single exposure to relevant information. Also, it is known that the algorithm used to transform the rated interest in Camel Snus into probabilities of use tends to over-estimate actual use (New Tobacco Product 'Likelihood' Study: An Algorithm to Predict Usage of New Tobacco Products Prior to Market Launch – Methodological Report). Finally, the projected probabilities of use represent a projected trial of Camel Snus and do not account for consumers' reactions to the actual product, which may lead to discontinuation rather than persistent use. However, the interest here is not in precisely estimating the absolute rates of use, but rather in estimating when such use results in beneficial versus harmful effects on population health. It is important to note that the key factor in balancing population benefit versus harm is the *relative* appeal of Camel Snus to various populations (*i.e.*, those that stand to benefit or be harmed). The likelihood of use studies provided estimates of that relative appeal. Therefore, even if the true values of Camel Snus adoption are lower than those estimated from the likelihood of use studies, the conclusion of whether a Camel Snus MRTP confers benefit or harm will be valid. This is demonstrated in a sensitivity analysis that assessed the effect of reducing the empirically estimated primary tobacco use transition rates by 75% (while leaving secondary transition rates unchanged). (The sensitivity analysis is documented in Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report.)

6.4.2.2.1.2 Using extreme inputs to estimate tipping points in the net population health impact of Camel Snus availability as an MRTP

The DPM(+1) modeler, utilizing inputs from the likelihood of use studies described above, aims to estimate the most likely net population health effects of the commercial availability of Camel Snus with modified risk advertising. In contrast, tipping point analyses that do not rely on empirically-derived model inputs but instead use extreme values address a conceptual question – At what point in a range of model inputs does the DPM(+1) predict a cross-over point between net population harm versus benefit? In particular, because the greatest benefit to population health is expected to derive from smokers switching completely to Camel Snus (as confirmed by the model output), the tipping point analyses address the conceptual question – How much switching of smokers to Camel Snus is necessary to yield enough

population benefit to overcome any harm that could occur from use of Camel Snus among non-smokers or those who would have quit smoking?

6.4.2.3 Modeled changes in population tobacco use

The DPM(+1) includes all of the major transitions in tobacco use behavior that might affect population mortality, comparing the counterfactual scenario where Camel Snus is available as an MRTP to the base case, where it is not. This section outlines the tobacco use transitions incorporated in the model, considering the likelihood of adoption of Camel Snus by various subgroups of individuals within the population. Table 6.4.2-1 identifies multiple possible transitions in tobacco use behaviors. The transitions in the counterfactual scenario are classified as harmful or beneficial to the affected individuals as compared to the base case where transitions to or from Camel Snus are not available (*i.e.*, where the only transition is between smoking and abstinence). Subsequent sections describe how the probability of each of these tobacco use transitions is assessed by the DPM(+1), when using execution-specific empirically-derived estimates from the likelihood of use studies and when performing analyses to estimate tipping points in population health effects. Each tobacco use transition is designated as primary or secondary (the first column) and given a brief descriptor that is used in the discussion that follows. These descriptors are capitalized and set in *italic* font to identify their usage in this specific technical way.

Table 6.4.2-1: Tobacco use transitions

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact: Benefit or Harm
Primary	Initiation with Camel Snus (instead of abstinence) by never users of tobacco who were *not* likely to initiate smoking	*Additional Initiation*	Harm
Secondary	--- Subsequent progression to smoking due to use of Camel Snus	*Gateway Effect*	Harm
Secondary	--- Subsequent cessation of Camel Snus‡		Benefit
Primary	Initiation with Camel Snus (instead of smoking) by never users of tobacco who *were* otherwise likely to initiate smoking	*Alternative Initiation*	Benefit
Secondary	--- Subsequent initiation of smoking due to use of Camel Snus	*Delayed Smoking*	Harm†
Secondary	--- Subsequent cessation of Camel Snus‡		Benefit
Primary	Adoption of Camel Snus (instead of smoking) by smokers who were *not* likely to quit	*Switching*	Benefit
Secondary	--- Subsequent return to smoking♦	*Resumed Smoking*	Harm†
Secondary	--- Subsequent cessation of Camel Snus‡		Benefit
Primary	Adoption of Camel Snus by smokers who were likely to quit, who either switch to Camel Snus instead of quitting¶ or who quit, then adopt Camel Snus*	*Diversion from Quitting*	Harm
Secondary	--- Subsequent relapse to smoking**	*Relapse*	Harm
Secondary	--- Subsequent cessation of Camel Snus‡		Benefit

--- Indicates a secondary transition among the population undergoing the primary transition immediately above.

‡ This secondary tobacco use transition is not considered in these analyses because no data are available to estimate the rate at which this transition would occur. This approach is conservative, as it does not consider health benefits that could accrue from quitting Camel Snus.

† This secondary transition is not net-harmful but rather reduces the benefit of the prior primary transition. For example, if a certain proportion of smokers *Switching* quickly go back to smoking (*Resumed Smoking*), this negates the benefit of *Switching* for that subset, yet they are no worse off than they were before trying Camel Snus.

♦These analyses treat smokers who initially switch to Camel Snus but then return to smoking as though they never use Camel Snus at all, rendering this secondary tobacco use transition neutral in effect (the affected individuals were smoking before the transition and are smoking after the transition). That is, a return to smoking was treated as a reversal of Switching, discounting the estimated Switching rate. This is conservative, as it does not consider any benefit due to a limited period of use of Camel Snus versus continued smoking.

¶ These analyses do not consider the potential that adoption of Camel Snus might delay rather than completely deter smoking cessation. This is conservative, as it does not count any health benefit that would come from smoking cessation, even if cessation were delayed.

* Smokers who quit and then adopt Camel Snus are modeled as never having quit smoking, with no health benefit attributed to quitting. In essence, these analyses assume these smokers never quit, but adopt Camel Snus instead of quitting.

** The modeler cannot directly accommodate individuals who quit, adopt Camel Snus, and then *Relapse* to smoking within the same age interval. To model *Relapse*, the model was run with the likelihood of quitting reduced, which has roughly the same effect as having a certain proportion of quitters instead continuing to smoke. This is conservative, as it does not account for any benefit of a period of smoking abstinence or use of Camel Snus. To discern the impact of *Relapse*, survival in the counterfactual scenario of this run of the model is compared to survival in the counterfactual scenario of a corresponding run of the model that does not include this effect. The difference in estimates between these two runs of the model is then used to adjust the estimated survival in analyses meant to include *Relapse*.

Figure 6.4.2-1 and Figure 6.4.2-2 schematically and heuristically portray the transitions that are considered in the analyses presented here[6]. As described in more detail in the figures, members of the cohort enter the process as non-tobacco users at age 13. The cohort consists of some members who are, by disposition, headed towards smoking, some of whom will initiate smoking (shown as "smoking initiation"), while others will instead initiate their tobacco use with Camel Snus (designated as *Alternative Initiation*[7]). Some of those in the *Alternative Initiation* group may eventually proceed onto smoking (designated as *Delayed Smoking*). The remainder of the cohort consists of individuals who are not, by disposition, headed toward smoking. Some of these individuals remain never-users of tobacco (shown as "non-initiation"). Other individuals take up Camel Snus, and this represents *Additional Initiation* – tobacco use that would not have occurred but for the availability of Camel Snus as an MRTP. Some of those in the *Additional Initiation* group may further proceed to smoking, which is designated as *Gateway Effect*.

Among those who take up smoking, further tobacco use transitions can occur within each 5-year age interval (Figure 6.4.2-2). In any age interval, certain transitions in tobacco use can occur. Some individuals who are not headed toward quitting continue to smoke (shown as "continued smoking"). Other individuals switch completely from smoking to Camel Snus (*Switching*), yet some of these individuals who switch may eventually resume smoking (*Resumed Smoking*) and are not considered to have switched at all. Dual use is modeled as having no health benefit – that is, it assumes dual users have the same risk as smokers, thus individuals engaging in dual use are simply considered continuing smokers. Other smokers who are headed toward quitting (*i.e.*, they would quit if the Camel Snus MRTP were not available) do quit smoking (shown as "quitting"). Others, though, adopt Camel Snus instead of quitting or after a brief period of quitting (*Diversion from Quitting*). For some who follow the *Diversion from Quitting* transition, their use of Camel Snus may result in *Relapse* to smoking.

Thus, the analyses presented here consider the full range of transitions in tobacco use, both harmful and beneficial, and, ultimately, their net effect on population health, expressed as changes in survival to age 72.

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[6] It is important to note that Figures 1a and 1b do not represent how the DPM(+1) models the transitions. They are a simplification of the counterfactual scenario and do not clearly distinguish the base case flow between tobacco use states. The reports submitted with this Application in Section 7 (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report; Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report) provide a technically accurate account of the transitions incorporated in the DPM(+1) in the base case and counterfactual scenarios. This schematic is intended only to help portray and label the transitions used in the analyses presented here heuristically.

[7] Transitions with capitalized and italicized labels represent the transitions that are considered as inputs to counterfactual scenario in the DPM(+1). Subsequent sections describe how these tobacco use transitions are estimated or posited in the modeler.

Figure 6.4.2-1: Schematic of the tobacco use initiation transitions in the DPM(+1)

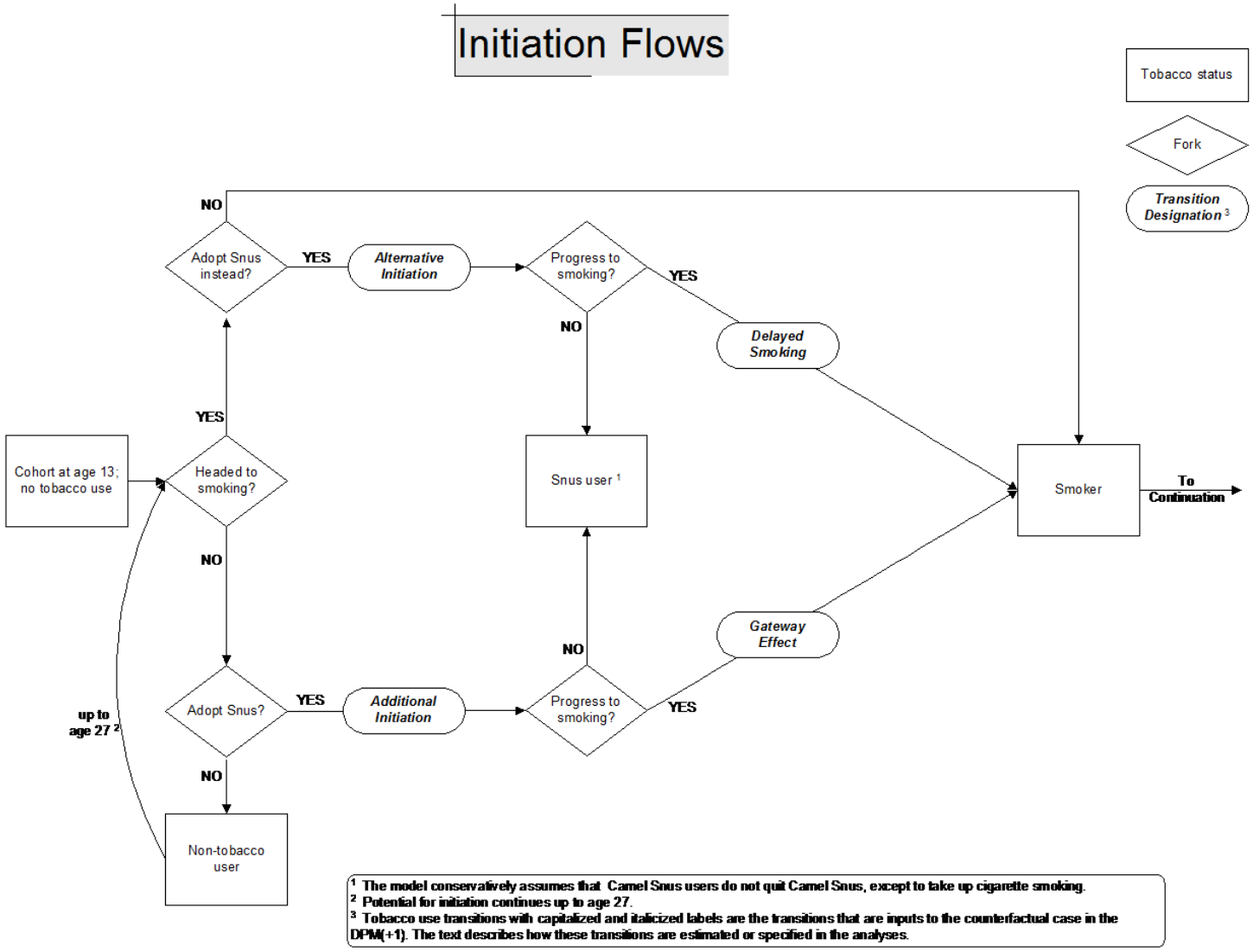
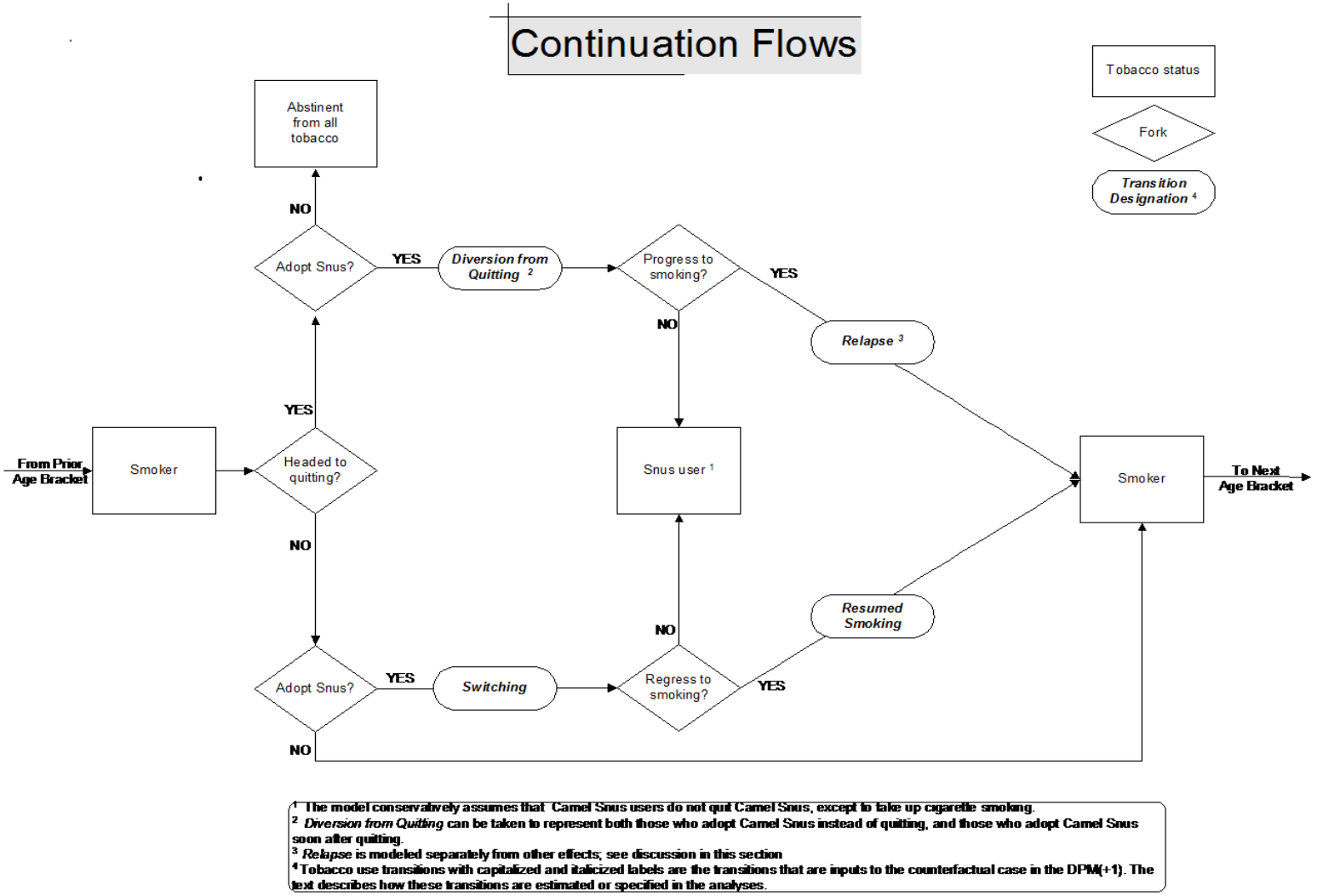


Figure 6.4.2-2: Schematic of the tobacco use continuation transitions in the DPM(+1)



The next several sections describe the DPM(+1) inputs used for each of the tobacco use transitions shown Table 6.4.2-1 and Figure 6.4.2-1 and Figure 6.4.2-2 above. As the DPM(+1) models the trajectory of a cohort that is initially not using tobacco, we begin with transitions involving adoption of Camel Snus by individuals who are not smoking or using any tobacco (that is, initiation with Camel Snus).

6.4.2.3.1 Initiation Flows in the DPM(+1)

The statistical modeling considers the health effects of adoption of Camel Snus by individuals who have not previously used tobacco, that is, initiation with Camel Snus. This situation would have an adverse effect on health when it occurs among individuals who would not otherwise have taken up smoking (*i.e.*, *Additional Initiation*). The adverse health effect is even greater if starting to use Camel Snus causes some of those individuals to subsequently progress to smoking (*i.e.*, *Gateway Effect*). Conversely, the effect of adopting Camel Snus can be favorable if it is taken up by someone who otherwise would have smoked (*i.e.*, *Alternative Initiation*), as it puts them on a lower health risk trajectory compared to having initiated smoking instead. Even if such individuals subsequently do take up smoking (as they were, by the definition of this group, expected to do), they may accrue some health benefit due to the delay in the onset of smoking (*i.e.*, *Delayed Smoking*). The following sections describe how the DPM(+1) incorporates these Initiation Flows.

6.4.2.3.1.1 Additional Initiation

Although Camel Snus presents less risk for lung cancer, oral cancer, respiratory disease and heart disease than cigarettes, it still carries some risk. Accordingly, an individual who otherwise would not have used tobacco, but who adopts Camel Snus as a result of exposure to the MRTP advertising is considered to be harmed. Such *Additional Initiation* is modeled based on both empirically-derived estimates (based on the likelihood of use study) and on extreme values employed to estimate tipping points.

Additional Initiation: Empirically-derived estimates

In the likelihood of use study, respondents who had never used tobacco estimated their likelihood of using Camel Snus. To distinguish between non-tobacco users who would have been likely versus unlikely to start smoking even if Camel Snus were not available, the non-tobacco users were assessed on measures of susceptibility to smoking (Pierce *et al*. 1996). The likelihood of use study assessed interest in trying Camel Snus across age ranges. However, based on consistent historical experience with tobacco initiation, it was considered that initiation is highly unlikely after age 26 (USDHHS 2012). Accordingly, the model applies the average projected rate of trial for ages 18-27 to each of the first three 5-year age intervals in the model: 13-17, 18-22, and 23-27.

Additional Initiation: Tipping point analyses

Two extreme values for *Additional Initiation* are used in tipping point analyses. One posits a value 10 times higher than that derived from empirical data. Another value posits the extreme hypothetical wherein rates of *Additional Initiation* with Camel Snus are as high as initiation rates into smoking, in contrast to the empirical data suggesting a much higher initiation rate for smoking than smokeless tobacco (USDHHS 2012).

6.4.2.3.1.2 Gateway Effect

Use of Camel Snus by individuals who would not otherwise have used tobacco causes harm because use of Camel Snus is more harmful than not using tobacco products at all. However, the harm is substantially increased if the adoption of Camel Snus leads to subsequent initiation of smoking (*Gateway Effect*), which carries much greater health risks. *Gateway Effect* is modeled by having the affected individuals transition directly into smoking at the next age interval after they initiate with Camel Snus.

Gateway Effect: Parameters used in empirically-based models

It was considered that the likelihood of a *Gateway Effect* could not be reliably estimated empirically from the likelihood of use study for two reasons. First, estimating such an effect requires respondents to speculate about two sequential hypotheticals: first they had to estimate their likelihood of adopting Camel Snus, and then, without even having actually tried Camel Snus, they had to further estimate the likelihood that they would later progress to smoking. Second, while respondent ratings of the likelihood of this secondary tobacco use transition could be (and were) obtained, there was no validated model for converting those likelihood estimates into projected probabilities of the tobacco use transition. Therefore, this secondary tobacco use transition is modeled by positing a 50% likelihood of occurring within the *Additional Initiation* population, which is the predicate group for *Gateway Effect* (that is, *Gateway Effect* occurs only within the *Additional Initiation* population).

Gateway Effect: Tipping point analyses

In tipping point analyses of *Additional Initiation*, *Gateway Effect* is posited to be 50%, an extreme value that results in conservative estimates of population health effects.

6.4.2.3.1.3 Alternative Initiation

The MRTP advertising proposed for Camel Snus is aimed at current smokers and is not meant to attract non-users of tobacco. However, for complete modeling of population health effects, it is important to consider that some non-tobacco users who would otherwise have initiated smoking might instead initiate tobacco use with Camel Snus. This hypothetical subgroup would experience a decrease in their relative health risk compared to the alternative course of becoming smokers.

Alternative Initiation: Empirically-derived estimates

Several steps were taken to estimate the likelihood of *Alternative Initiation* as defined above. First, never tobacco users demonstrating susceptibility to smoke (Pierce *et al*. 1996) rated their likelihood to try Camel Snus after viewing the proposed modified risk advertising. Those ratings, in turn, were transformed into projected likelihoods of use of Camel Snus. While ratings were made by respondents of all ages, based on consistent historical experience with tobacco initiation in the U.S., it was considered that initiation is highly unlikely after age 26 (USDHHS 2012). Accordingly, the model applies the likelihood of use estimated for ages 18-27 to each of the first three 5-year age intervals in the model: 13-17, 18-22, and 23-27.

Alternative Initiation: Tipping point analyses

The health benefit associated with *Alternative Initiation* is not included in tipping point analyses because the focus of these analyses is to assess when the potential benefits of *Switching* are sufficient to overcome the posited harmful tobacco use transitions.

6.4.2.3.1.4 Delayed Smoking

The statistical modeling also considers that some individuals who engage in *Alternative Initiation* might later progress to smoking (as they were originally anticipated to do). This group might still experience some health benefit (relative to the course they otherwise would have taken) due to the delay in adoption of smoking, but the benefit would be considerably reduced. In any case, *Delayed Smoking* represents adoption of smoking by individuals who were otherwise expected to smoke, so this secondary tobacco use transition represents a reduction in the benefit due to *Alternative Initiation* rather than direct harm.

Delayed Smoking: Parameters used in empirically-based models

It was considered that the likelihood of *Delayed Smoking* could not reliably be estimated from the likelihood of use study for two reasons. First, it requires respondents to speculate about two sequential hypotheticals: first their likelihood of adopting Camel Snus, and then, without even having actually tried Camel Snus, the likelihood that they would later progress to smoking. Second, while respondent ratings of the likelihood of this secondary tobacco use transition could be (and were) obtained, there was no validated model for converting those likelihood estimates into projected probabilities of the tobacco use transition. Therefore, this secondary tobacco use transition is modeled by positing a 50% likelihood of occurring within the *Alternative Initiation* population, which is the predicate group for *Delayed Smoking* as *Delayed Smoking* can only occur following *Alternative Initiation* (this approach parallels the value used to model secondary *Gateway Effect* following *Additional Initiation*).

Delayed Smoking: Tipping point analyses

Tipping point analyses do not include *Alternative Initiation*, a beneficial transition that is the predicate for *Delayed Smoking* (*i.e.*, this transition is only possible for those who engage in

Alternative Initiation). Thus, *Delayed Smoking* (which does not introduce new harms but simply reduces the beneficial effect of *Alternative Initiation*) is not included in the tipping point analyses.

6.4.2.3.2 Continuation Flows in the DPM(+1)

Over time, a proportion of the population initiates and adopts smoking. The DPM(+1) incorporates empirically-derived rates of smoking initiation from population data (Table 6.4.1-1) and considers the health effects of adoption of Camel Snus by individuals who are already smoking. Adoption of Camel Snus by a smoker would have an adverse effect on health if it occurs among individuals who are intending to quit tobacco use completely (*i.e.*, *Diversion from Quitting*). The adverse health effect would be even greater if *Diversion from Quitting* results in return to smoking cigarettes (*i.e.*, *Relapse*). Conversely, the effect of adopting Camel Snus can be favorable if it is taken up by a smoker who is not intending to quit smoking (*i.e.*, *Switching*), as it puts them on a lower health risk trajectory compared with continuing to smoke. A return to smoking among those *Switching* to Camel Snus (*i.e.*, *Resumed Smoking*) would result in less benefit than if they had continued using Camel Snus or stopped all tobacco use. The following sections describe how the DPM(+1) incorporates these Continuation Flows.

6.4.2.3.2.1 Switching

Switching: Empirically-derived estimates

Smokers in the likelihood of use study whose survey responses indicated that they were not likely to quit smoking were used to generate empirically-derived estimates of *Switching* probabilities. The likelihood of *Switching* declines with age, and age-specific rates are used in the DPM(+1) modeling.

Switching: Tipping point analyses

Causing smokers who are not ready to quit smoking to switch completely to Camel Snus (*Switching*) is the primary behavioral target for the modified risk advertising. Indeed, as noted above and discussed in detail below, the statistical modeling confirms that *Switching* is the tobacco use transition associated with the greatest net population health benefit. Accordingly, it was the focus of tipping point analyses. In line with this, tipping point analyses did not pre-specify a probability of *Switching*, but rather used modeling to determine what rate of persistent *Switching* would be needed in each 5-year age interval to produce a neutral or positive net population health effect in the face of either empirically-derived probabilities or high probabilities of otherwise harmful tobacco use transitions. That is, the tipping point analyses aim to define probabilities of *Switching* as an outcome of the statistical modeling, rather than positing them as inputs to the model.

6.4.2.3.2.2 Resumed Smoking

Resumed Smoking: Empirically-derived estimates

The statistical modeling also considers that some smokers who switch to Camel Snus might quickly (*i.e.*, within the same age interval and without gaining any health benefit) return to smoking (or dual use). It was considered that the likelihood of *Resumed Smoking* could not reliably be estimated empirically from the likelihood of use study for two reasons. First, estimating such an effect requires respondents to speculate about two sequential hypotheticals: first they had to estimate their likelihood of adopting Camel Snus, and then, without even having actually tried Camel Snus, they had to further estimate the likelihood that they would later return to smoking. Second, while respondent ratings of the likelihood of this secondary tobacco use transition could be (and were) obtained, there is no validated model for converting those likelihood estimates into projected probabilities of this transition. Therefore, this secondary tobacco use transition is modeled by positing a 50% likelihood of occurrence within the *Switching* population, which is the predicate for *Resumed Smoking* (that is, *Resumed Smoking* occurs only within the *Switching* population).

Resumed Smoking: Tipping point analyses

Tipping point analyses assess the amount of persistent *Switching* in each 5-year age interval needed to offset various harms. As *Resumed Smoking* is a discount of some proportion of the smokers *Switching*, its effect is to proportionately increase the tipping point. Thus, if *Resumed Smoking* is considered to be 50%, the tipping point would need to be doubled.

6.4.2.3.2.3 Diversion from Quitting

Camel Snus is less harmful than smoking, so smokers who switch to Camel Snus instead of continuing to smoke gain a health benefit. However, use of Camel Snus still has some risk, and quitting all tobacco use is the safest course for a smoker. Accordingly, if smokers switch to Camel Snus instead of quitting (*Diversion from Quitting*), they would be harmed compared to the health effects they would have experienced had they quit tobacco use completely.

Diversion from Quitting: Empirically-derived estimates

The likelihood of use study provides empirically-derived estimates of *Diversion from Quitting*, based on the projected adoption of Camel Snus among smokers who were deemed likely to quit, as assessed from their recent quitting behavior, expressed interest in quitting, and confidence that they could quit successfully (Hyland *et al*. 2006). The projected likelihood of use of Camel Snus among those smokers likely to quit varies by age, and age-specific rates are applied in the modeling.

Diversion from Quitting: Tipping point analyses

To assess the tipping point when *Diversion from Quitting* is set to an extreme value, the DPM(+1) input for *Diversion from Quitting* is set at 50%, to assess how much persistent

Switching in each 5-year age interval would be necessary to overcome this adverse effect in order to produce a neutral or positive net effect on population health.

6.4.2.3.2.4 Relapse

As stated above, smokers in the *Diversion from Quitting* group who would otherwise have quit all tobacco use but instead adopt Camel Snus are harmed because they suffer the incremental risk of using tobacco instead of quitting tobacco use entirely. However, their residual health risk is still much smaller than if they had continued to smoke (as long as they continue using Camel Snus and do not resume smoking). If some of these smokers subsequently return to smoking (*Relapse*) as a result of adopting Camel Snus, this would increase harm.

The effect of *Relapse* after quitting within the same age interval cannot be directly assessed within the complex DPM(+1) modeler because individuals can only transition between tobacco use states once within an age interval. However, the effect of *Relapse* within the same age interval can be estimated by comparing two counterfactual scenarios — one that allows smoking cessation but reduces the number of smokers quitting to take *Relapse* into account (*i.e.*, by treating those individuals as never having quit smoking) to another where the smoking cessation rate remains unchanged. The result of the comparison of these two scenarios is then used to adjust the expected impact on survival from models that were meant to include the *Relapse* effect.

Relapse: Empirically-derived estimates

It was considered that the likelihood of *Relapse* could not be reliably estimated from the likelihood of use study for two reasons. First, it requires respondents to speculate about two sequential hypotheticals: first their likelihood of adopting Camel Snus, and then, without even having actually tried Camel Snus, to estimate the likelihood that they would later return to smoking. Second, while respondent ratings of the likelihood of this secondary transition could be (and were) obtained, there is no validated model for converting those likelihood ratings into projected probabilities of a subsequent tobacco use transition back to smoking. Therefore, this secondary tobacco use transition is modeled by positing a high likelihood of 50%.

Relapse: Tipping point analyses

Because *Relapse* cannot be integrated into the model, the effects of *Relapse* are not tested in separate tipping point analyses. *Relapse* effects are incorporated in tipping point analyses by discounting the population benefit in accordance with separate estimates of the effects of *Relapse* on the population impact.

6.4.2.3.3 Simultaneous modeling of all inputs and identifying effects of particular component inputs

For analyses using empirically-derived inputs as well as for tipping point analyses that input empirically-derived and extreme values, the DPM(+1) is used to model a counterfactual

scenario that includes all of the tobacco use transitions listed in Table 6.4.3-1 and the estimates presented in that table. We refer to this as the Master model. The Master model aims to model a fleshed-out counterfactual scenario that simultaneously incorporates all of the inputs outlined above. It provides a global and summative sense of the overall population health effect of the Camel Snus MRTP with modified risk advertising.

However, such a complex and multifaceted statistical model does not provide a clear view of the impact of each of the individual component inputs to the model (*i.e.*, which inputs have greater or lesser impact on the population health effects). In order to provide such insights, the DPM(+1) is also used to assess certain inputs individually. These more limited Component analyses do not represent the full range of anticipated effects actually expected to occur, but rather, by isolating the effect of particular model inputs, lend insight into the absolute and relative contributions of the individual inputs.

6.4.2.3.4 Modeling population impact of a Camel Snus MRTP based on specific modified risk advertising executions

This section has described the modeling procedures and assumptions used to estimate the impact of a Camel Snus MRTP on population health. These processes are applied, and models run separately, for each of the three executions of the proposed modified risk advertising for Camel Snus because each of the three executions was tested in a likelihood of use study, and each study yielded different estimates of primary transitions in tobacco use behaviors. Accordingly, the sections that follow present each execution separately and report the modeling inputs based on that execution's performance in its likelihood of use study and the resulting model estimates.

6.4.3 Modeling Results for Execution 1

The proposed modified risk advertisement presented in Execution 1 included claims for significantly reduced risk of lung cancer, oral cancer, respiratory disease, and heart disease for smokers who switched completely from using cigarettes to Camel Snus. This section provides results of the modeling conducted for Execution 1 (complete statistical modeling results for Execution 1 are in Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report). To assess the likely impact of the advertising presented in Execution 1, the DPM(+1) modeler uses the estimates of Camel Snus use from the likelihood of use study Execution 1, as described below.

6.4.3.1 Model using empirically-derived estimates

6.4.3.1.1 Modeler inputs

The DPM(+1) modeler uses empirically-derived estimates as inputs for the probability of all primary tobacco use transitions, based on results of the likelihood of use study Execution 1 (Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-

Users – *First Execution of Consumer Testing* – Amended Final Report). Individuals with varying tobacco use status were shown the proposed Camel Snus MRTP advertising and rated their interest in trying Camel Snus (likelihood of purchase for trial). These ratings were converted into likelihood of use probabilities (*i.e.*, likelihood of purchase), which formed the basis for the empirical estimates of primary tobacco use transitions. Table 6.4.3-1 below shows the inputs to the model. *Switching* is posited to range from 16.5% to 1.7%, decreasing over successive 5-year age intervals (see Table 6.4.3-1 below and Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *First Execution of Consumer Testing* – Amended Final Report); *Diversion from Quitting* similarly varies by age, from 20.0% to 1.8%, generally decreasing by age. *Additional Initiation* is estimated at 0.3%, and *Alternative Initiation* at 0.5% for the 13-27 age intervals, based on the empirically-derived projections from the likelihood of use study among respondents ages 18-27 years. Secondary tobacco use transitions (*Gateway Effect, Delayed Smoking, Resumed Smoking,* and *Relapse*) cannot be projected from the likelihood of use study, and are thus included in the analyses as hypothetical (and in many instances, extreme) values, with a 50% probability of occurring.

6.4.3.1.2 Summary of results, Execution 1

Using the inputs in Table 6.4.3-1, which incorporate the findings of the likelihood of use study for Execution 1, a series of analyses were run. The results or outputs of the analyses are summarized in Table 6.4.3-2, which shows the estimated effect on survival at age 72 for a hypothetical cohort of one million males[8]. The entries represent the difference in survival between the counterfactual scenario (where some portion of the population uses Camel Snus as an MRTP) and the base case (where only cigarette smoking is an available tobacco use option). Positive numbers indicate improved survival and a benefit to population health in the counterfactual scenario; negative numbers indicate reduced survival and harm to population health. Also shown are the 95% Posterior Intervals (PI), which take into account the uncertainty posited for the input estimates to the base case model, as well as the estimated ERR for Camel Snus. Table 6.4.3-2 shows separate estimates, assuming an ERR of 0.11 and 0.08. Each row represents a set of model inputs, starting with the Master model, which includes almost all the transitions shown in Table 6.4.3-1, followed by Component analyses that isolate particular tobacco use transitions in order to provide insight on the impact of each transition. Primary tobacco use transitions are considered singly. Secondary tobacco use transitions are considered together with their predicate primary transitions. For example, *Gateway Effect* (a secondary transition) can only occur after *Additional Initiation* (a primary transition). Therefore, one analysis considers *Additional Initiation* on its own, and another analysis adds *Gateway Effect*, whose individual contribution can be estimated as the difference between the two analyses. Each analysis is discussed briefly, with reference to Table 6.4.3-1 and Table 6.4.3-2.

[8] The DPM(+1) modeler is run on a hypothetical population of 1 million males. Since U.S. birth cohorts are actually about 4.1 million, 51% of whom are female (U.S. Census Bureau 2016), survival estimates are also provided for this more representative mixed-gender birth cohort.

Table 6.4.3-1: DPM(+1) inputs for the probability of tobacco use transitions, Execution 1

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact: Benefit or Harm	Modeled Probability	
Primary	Initiation with Camel Snus (instead of abstinence) by never users of tobacco who were *not* likely to initiate smoking	*Additional Initiation*	Harm	0.3%[a]	
Secondary	--- Subsequent progression to smoking due to use of Camel Snus	*Gateway Effect*	Harm	50%[d]	
Primary	Initiation with Camel Snus (instead of smoking) by never users of tobacco who *were* otherwise likely to initiate smoking	*Alternative Initiation*	Benefit	0.5%[a]	
Secondary	--- Subsequent initiation of smoking	*Delayed Smoking*	Harm†	50%[d]	
Primary	Adoption of Camel Snus (instead of smoking) by smokers who were *not* likely to quit	*Switching*	Benefit	**Age Interval**	**% Switching to Camel Snus**
				18-22	16.5
				23-27	10.9
				28-32	8.8
				33-37	7.4
				38-42	4.7
				43-47	5.5
				48-52	4.5
				53-57	2.2
				58-62	2.6
				63-67	2.4
				68+	1.7
Secondary	--- Subsequent return to smoking♦	*Resumed Smoking*	Harm†	50%[b]	

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact: Benefit or Harm	Modeled Probability	
				Age Interval	% Using Camel Snus
Primary	Adoption of Camel Snus by smokers who were likely to quit, who either switch to Camel Snus instead of quitting[¶] or who quit, then adopt Camel Snus*	*Diversion from Quitting*	Harm	18-22	20.0
				23-27	8.6
				28-32	6.5
				33-37	4.5
				38-42	7.4
				43-47	5.4
				48-52	5.5
				53-57	2.9
				58-62	1.8
				63-67	2.1
				68+	2.1
Secondary	--- Subsequent relapse to smoking**	*Relapse*	Harm	50%[c]	

--- Indicates a secondary transition among the population undergoing the primary transition immediately above.

† This secondary transition is not net-harmful but rather reduces the benefit of the prior primary transition. For example, if a certain proportion of smokers *Switching* quickly go back to smoking (*Resumed Smoking*), this negates the benefit of *Switching* for that subset, yet they are no worse off than they were before trying Camel Snus.

♦These analyses treat smokers who initially switch to Camel Snus but then return to smoking as though they never use Camel Snus at all, rendering this secondary tobacco use transition neutral in effect (the affected individuals were smoking before the transition and are smoking after the transition). That is, a return to smoking was treated as a reversal of *Switching*, discounting the estimated *Switching* rate. This is conservative, as it does not consider any benefit due to a limited period of use of Camel Snus versus continued smoking.

¶ These analyses do not consider the potential that adoption of Camel Snus might delay rather than completely deter smoking cessation. This is conservative, as it does not count any health benefit that would come from smoking cessation, even if cessation were delayed.

* Smokers who quit and then adopt Camel Snus are modeled as never having quit smoking, with no health benefit attributed to quitting. In essence, these analyses assume these smokers never quit, but adopt Camel Snus instead of quitting.

** The modeler cannot directly accommodate individuals who quit, adopt Camel Snus, and then *Relapse* to smoking within the same age interval. To model *Relapse*, the model was run with the likelihood of quitting reduced, which has roughly the same effect as having a certain proportion of quitters instead

continuing to smoke. This is conservative, as it does not account for any benefit of a period of smoking abstinence or use of Camel Snus. To discern the impact of *Relapse*, survival in in the counterfactual scenario of this run of the model is compared to survival in in the counterfactual scenario of a corresponding run of the model that does not include this effect. The difference in estimates between these two runs of the model is then used to adjust the estimated survival in analyses meant to include the *Relapse* effect.

[a] Applies only to ages 13-27
[b] Not empirically-derived; conservative estimate; reverses percentage of *Switching*
[c] Analyzed separately from other tobacco use transitions with results used to adjust projected survival; transition is not included in the Master model
[d] Applies only to ages 18-32; not empirically-derived; conservative estimate

Table 6.4.3-2: Estimated changes in survival to age 72 in a hypothetical cohort of one million males, followed from age 13 to age 72

	ERR = 0.11			ERR = 0.08		
Model	**Estimated change in survival**	**95% Posterior Interval**		**Estimated change in survival**	**95% Posterior Interval**	
		Min	**Max**		**Min**	**Max**
Master model	5,751	4,994	6,524	6,196	5,398	7,015
Master model, with *Relapse* ♦	5,035			5,445		
Component analyses††						
Switching	11,864	10,449	13,292	12,476	10,991	13,971
Switching with *Resumed Smoking**	6,450	5,683	7,229	6,781	5,976	7,595
Diversion from Quitting	-318	-277	-362	-235	-204	-266
Diversion from Quitting with *Relapse** ♦	-1,177			-1,135		
Alternative Initiation	80	68	93	91	78	105
Alternative Initiation with *Delayed Smoking**	45	36	55	51	41	61
Additional Initiation	-205	-193	-217	-145	-134	-155
Additional Initiation with *Gateway Effect**	-415	-397	-435	-382	-364	-400

†† Refer to the tobacco use transitions in Table 6.4.3-1 where each tobacco use transition is described.

* Analyses that include secondary tobacco use transitions necessarily must also include their predicate primary transitions. The impact of the secondary transition can be estimated by the difference in survival between the model run with the secondary transition and the model run with only the predicate primary transition.

♦ The estimated change in survival in these model runs incorporates *Relapse* effects. As discussed in this section, *Relapse* in the same age interval cannot be fully incorporated into the DPM(+1), but its effects can be estimated by comparing two counterfactual scenarios. The reduction in projected survival due to *Relapse* is used to reduce the projected survival estimates in model runs that include *Relapse* compared to the same model run without *Relapse*. However, because the difference between the counterfactual scenario and the base case is not estimated directly for counterfactual scenarios incorporating *Relapse*, 95% PIs are not provided.

6.4.3.1.3 Master model

6.4.3.1.3.1 Model specifications

The Master model incorporates all tobacco use transitions shown in Table 6.4.3-1, using the estimates of primary beneficial and harmful transitions derived from the likelihood of use study for Execution 1, and hypothetical (and in most instances, extreme) probabilities for secondary harmful transitions. Only *Relapse* (which separate analysis confirmed has relatively small effect) is omitted. Thus, this Master model incorporates all but one (*Relapse*) of the inputs defined in Table 6.4.3-1 and uses empirically-derived estimates from the likelihood of use study Execution 1 for all primary tobacco use transitions.

6.4.3.1.3.2 Model estimates

Table 6.4.3-2 shows the survival predictions from the Master model, which is run on a hypothetical cohort of one million 13-year-old males.

Master Model. This model includes all harmful and beneficial tobacco use transitions, with the exception of *Relapse* in the same age interval, which cannot be integrated into the model. Using the more conservative ERR of 0.11, the model projects a benefit of 5,751 additional survivors [95% PI: 4,994 to 6,524] at age 72 for the counterfactual scenario (Camel Snus MRTP available) versus base case (cigarettes only available). Using an ERR of 0.08 yields slightly more favorable results, with an estimated 6,196 survivors [95% PI: 5,398 to 7,015] – that is, 445, or 7.7%, more survivors to age 72 than the model with the ERR of 0.11.

Master Model with Relapse. Although *Relapse* in the same age interval cannot be integrated into the Master model, the resulting estimate can be adjusted for *Relapse* effects, which are assessed separately. The *Relapse* adjustment reduces the estimated net survival to 5,035 for an ERR=0.11 and to 5,445 for an ERR=0.08.

Therefore, analyses that incorporate all primary harmful tobacco use transitions (based on empirically-derived estimates) and all harmful secondary transitions (based on hypothetical, and, in many instances, extreme, estimates) project the Camel Snus MRTP to result in substantial benefit to population health with approximately 6,000 additional survivors in a single birth cohort.

6.4.3.1.3.3 Sensitivity testing for the empirically-based estimates of transitions to Camel Snus

In the Master model, estimates empirically-derived from the likelihood of use study are used as assumptions about the probability of primary tobacco use transitions. These projections are based on self-reported interest in trying Camel Snus given by the study participants that are then applied to an empirical algorithm to estimate the probability of purchase for trial (New Tobacco Product 'Likelihood' Study: An Algorithm to Predict Usage of New Tobacco Products Prior to Market Launch – Methodological Report). Tests of the predictive algorithm indicated

that these projections may over-estimate the actual rate of transitions to use of Camel Snus. However, logically, consistently overestimating use of Camel Snus is not expected to change the conclusion that Camel Snus has a net positive effect on population health (survival), although it would be expected to change the magnitude of the benefit. The reasoning for this rests on the notion that adoption of Camel Snus is responsible for ***both*** the harms and the benefits in the model, with harms or benefits accruing depending on the population in question. So, if adoption of Camel Snus is lower than estimated, across the board, this would likely reduce both the benefits and harms proportionately, leaving unchanged the conclusion that a Camel Snus MRTP yields a population benefit, though reducing the magnitude of the benefit.

Therefore, a variation of the Master model was run in which all of the empirically-derived estimates of primary tobacco use transitions were reduced by 75%, while secondary transitions retained their original probabilities. As expected, that model run also yielded a net population benefit, with the magnitude of the benefit reduced by approximately 74% (1,639 additional survivors based on ERR=0.08, and 1,521 based on ERR=0.11). Thus, the conclusion that a Camel Snus MRTP is likely to benefit population health is robust to even extreme variations in the estimated appeal of Camel Snus, if, in fact, those variations are proportional.

6.4.3.1.4 Examining the contributions of different tobacco use transitions: Component analyses

The Master model assesses the joint effects of multiple tobacco use transitions on projected survival. The Component analyses that follow isolate the influence of specific components on survival. Thus, they do not represent, nor are they intended to represent, realistic scenarios but rather are included to provide conceptual insight into how the Master model inputs, considered in isolation, exert their influence on the model's outputs.

It should be noted that the effect of various components is not independent or additive; that is, one cannot simply sum the effects of all the components and derive the effects seen in the Master model. The different component parameters affect one another. For example, if *Additional Initiation* or *Alternative Initiation* increases, this results in fewer smokers in the next age interval, which in turn moderates the effect of subsequent transitions such as *Switching*.

6.4.3.1.4.1 Switching

Specifications

This Component analysis isolates the effect of *Switching*; that is, the effect of smokers who were not likely to quit smoking who switch completely to Camel Snus. This tobacco use transition confers a health benefit, because these individuals reduce their risk relative to continued smoking. *Switching* is estimated based on the likelihood of use study, which estimated the uptake of Camel Snus among smokers who were not likely to quit. The estimated rates of *Switching* decline with age and are assessed in an age-specific way.

Analysis estimates

As shown in Table 6.4.3-2, using the more conservative ERR of 0.11, *Switching* projects a survival benefit of 11,864 [95% PI: 10,449 to 13,292] additional survivors in the birth cohort. Using an ERR of 0.08 yields more favorable results with a projected 12,476 additional survivors [95% PI: 10,991 to 13,971] – approximately 600 more than when the ERR is 0.11 (an increase of 5%).

This analysis estimates the effect of smokers who were not likely to quit smoking who instead switch to Camel Snus, which substantially reduces their health risks. The estimated 12,000-person increase in survival is far greater than the figures estimated in the Master model that included many other tobacco use transitions, both beneficial and harmful. These analyses indicate that the effect of *Switching* is by far the tobacco use transition most affecting the population impact of a Camel Snus MRTP. (Accordingly, it is the focus of tipping point analyses presented subsequently.)

6.4.3.1.4.2 Resumed Smoking

Specifications

This Component analysis considered that some of the smokers not likely to quit who switch to Camel Snus instead of smoking would soon return to smoking. This secondary tobacco use transition would reduce the beneficial population impact of *Switching*. As this secondary tobacco use transition cannot be estimated from the likelihood of use data, it is assigned a probability of occurrence of 50% (*i.e.*, the impact of *Resumed Smoking* is estimated by reducing the empirically-derived estimate of *Switching* by 50%).

Analysis estimates

Table 6.4.3-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, a survival benefit of 6,450 [95% PI: 5,683 to 7,229] additional survivors is projected. Using an ERR of 0.08 yields more favorable results with a projected 6,781 additional survivors [95% PI: 5,976 to 7,595] – approximately 330 more than when the ERR is 0.11 (an increase of 5%).

Assuming that 50% of those *Switching* to Camel Snus quickly return to smoking reduces the projected survival benefit by almost half. (The reduction is slightly less than half because positing that half of those *Switching* return to smoking increases the pool of smokers who can subsequently quit smoking, whereas the model does not incorporate quitting of Camel Snus.) Nevertheless, *Switching*, even with *Resumed Smoking*, is estimated to improve survival to age 72 by at least 6,000 persons in the cohort.

6.4.3.1.4.3 Diversion from Quitting

Specifications

This Component analysis isolates the effect of *Diversion from Quitting*, which can be thought of as two potential mechanisms for harm – smokers who otherwise were expected to quit adopt Camel Snus instead of quitting, and smokers who actually do quit and then adopt Camel Snus instead of remaining tobacco free. In both cases, the result is assessed as harmful because Camel Snus carries more risk than abstinence from all tobacco use. Analyses do not distinguish between these two harms because of the assumption that any abstinence in these groups is short-lived and provides no health benefit.

The estimated rates of *Diversion from Quitting* are based on the likelihood of use study, which estimated uptake of Camel Snus among current smokers who were likely to quit. The estimates generally decline with age. Using only estimates from current smokers likely to quit is conservative because estimated rates of Camel Snus adoption among former smokers are much lower in the likelihood of use study (Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *First Execution of Consumer Testing* – Amended Final Report).

Analysis estimates

Table 6.4.3-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a deficit of 318 [95% PI: -277 to -362] fewer survivors. Using an ERR of 0.08 yields more favorable results with a projected 235 fewer survivors [95% PI: -204 to -266] – 83 more survivors than when the ERR is 0.11.

This analysis estimates the effect of taking up Camel Snus among smokers who were likely to quit smoking, which increases their risk compared to abstaining from all tobacco. The estimated reduction in survival is far smaller than the estimated increase in survival due to *Switching* among smokers who were not likely to quit (Table 6.4.3-2) because the increase in risk going from abstinence to use of Camel Snus is much smaller than the decrease in risk going from smoking to using Camel Snus. Furthermore, based on the results of the likelihood of use study, more smokers fall into the not-likely-to-quit group, and smokers who were likely to quit were less likely to adopt Camel Snus. This suggests that the increased survival due to *Switching* will overcome the harm due to *Diversion from Quitting* to yield a population benefit.

6.4.3.1.4.4 Relapse

Specifications

This Component analysis considers that some of the individuals in the *Diversion from Quitting* group – smokers who were expected to (or did) quit but adopted Camel Snus instead of complete abstinence from all tobacco – might resume smoking (*Relapse*). Individuals who *Relapse* would be substantially harmed because they incur the harms of smoking, which they

otherwise would have avoided but for their use of the MRTP. As described above, the impact of *Relapse*, estimated in a separate analysis, is used to adjust the estimated survival in the *Diversion from Quitting* analysis.

Because the probability of the secondary tobacco use transition of *Relapse* cannot be estimated empirically from the likelihood of use data, analyses include a conservative estimate of 50% of the *Diversion from Quitting* group who would *Relapse* to smoking.

Analysis estimates

Table 6.4.3-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11 and a very conservative estimate of *Relapse* at 50%, the projected survival is a deficit of 1,177 fewer survivors. The estimate (-1,135) is more favorable when the ERR is 0.08. Posterior Intervals cannot be computed for these *Relapse*-adjusted analyses.

These analyses show that, as expected, *Relapse* exacerbates the harm of *Diversion from Quitting*. For example, assuming an ERR of 0.11, *Relapse* decreases survival by 859 individuals in the cohort, compared to *Diversion from Quitting* without *Relapse*. This adverse effect is substantial. That it is substantially smaller than the expected beneficial effect of *Switching* suggests that it can be counteracted by sufficient *Switching* among smokers; this will be explored in the tipping point analyses, below.

6.4.3.1.4.5 Alternative Initiation

Specifications

This Component analysis isolates the effect of *Alternative Initiation* (uptake of Camel Snus among non-tobacco users aged 13-27 who were otherwise expected to take up smoking). This tobacco use transition confers a benefit because these individuals avoid the excess risk of smoking. *Alternative Initiation* is estimated from the likelihood of use study in which non-tobacco-using respondents who were assessed as susceptible to smoking estimated their likelihood to take up Camel Snus. Based on extensive documented evidence of tobacco initiation by age in the U.S. population, initiation was limited to ages 13-27, and *Alternative Initiation* is estimated at 0.5% within each of the three 5-year age intervals covering this age range.

Analysis estimates

Table 6.4.3-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a benefit of 80 [95% PI: 68 to 93] additional survivors. Using an ERR of 0.08 yields slightly more favorable results with a projected 91 [95% PI: 78 to 105] additional survivors – 11 more than when the ERR is 0.11.

Thus, in this analysis isolating the effect of *Alternative Initiation*, this tobacco use transition has a modest benefit of 80 additional survivors at age 72. Compared to the benefit estimated for

Switching, *Alternative Initiation* has a far more modest effect on survival within a single birth cohort.

6.4.3.1.4.6 Delayed Smoking

Specifications

This Component analysis considers that some individuals who engaged in *Alternative Initiation* – young non-tobacco users who were expected to smoke but instead initiated with Camel Snus – may nevertheless go on to smoke. This *Delayed Smoking* group may reap some benefit from its use of Camel Snus, because their onset of smoking is delayed, but the projected benefit would be less than that for those who continue to use Camel Snus and never go on to smoke.

Because the probability of this secondary tobacco use transition cannot be estimated empirically from the likelihood of use data, analyses assume that 50% of the *Alternative Initiation* group progress to smoking (this parallels the assumption used to assess *Gateway Effect*).

Analysis estimates

Table 6.4.3-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a benefit of 45 [95% PI: 36 to 55] additional survivors. Estimates are modestly higher when the ERR is 0.08 (estimated survival benefit of 51; 95% PI: 41 to 61).

These analyses show that, as expected, *Delayed Smoking* reduces the expected benefit from *Alternative Initiation*. For example, using an ERR of 0.11, *Alternative Initiation* is estimated to increase survival by 80 persons, but this is decreased to 45 if 50% eventually become smokers. Therefore, *Delayed Smoking* decreases the survival benefit of *Alternative Initiation*, while the posited transitions, in aggregate, would still provide a survival benefit.

6.4.3.1.4.7 Additional Initiation

Specifications

This Component analysis isolates the effect of *Additional Initiation* (uptake of Camel Snus among non-tobacco users aged 13-27 who were otherwise not expected to take up smoking). This tobacco use transition confers harm because these individuals would otherwise have avoided all tobacco-related harm. *Additional Initiation* is estimated from the likelihood of use study in which non-tobacco using respondents who were assessed as not being susceptible to smoking estimated their likelihood to take up Camel Snus. Based on extensive documented evidence of tobacco initiation by age in the U.S. population, initiation was limited to ages 13-27, and *Additional Initiation* was estimated at 0.3% within each of the three 5-year age intervals covering this age range.

Analysis estimates

Table 6.4.3-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a decrease of 205 [95% PI: -193 to -217] fewer survivors. Using an ERR of 0.08 yields slightly more favorable results with 145 [95% PI: -134 to -155] fewer survivors, which is 60 more survivors than when the ERR is 0.11.

This analysis suggests that *Additional Initiation*, as expected, has harmful effects on survival in the cohort population. Compared to the positive benefit of *Switching*, the effect is much smaller because *Additional Initiation* is a low-probability event, estimated at 0.3% in the first three 5-year age intervals, and also because the harmful effects of Camel Snus are much lower than those of smoking.

6.4.3.1.4.8 Gateway Effect

Specifications

This Component analysis considers that some of the individuals in the *Additional Initiation* cohort – young non-tobacco users who were not expected to smoke but did initiate with Camel Snus – might eventually begin smoking (*Gateway Effect*). Individuals who experience the *Gateway Effect* tobacco use transition would be substantially harmed because they incur the harms of smoking, which they otherwise would have avoided.

Because the probability of this secondary tobacco use transition cannot be estimated empirically from the likelihood of use data, analyses conservatively assume that 50% of the *Additional Initiation* group progress to smoking.

Analysis estimates

Table 6.4.3-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a decrease of 415 [95% PI: -397 to -435] fewer survivors. Estimates are more favorable when the ERR is 0.08 with 382 [95% PI: -364 to -400] fewer survivors.

These analyses show that, as expected, the *Gateway Effect* transition exacerbates the harm of *Additional Initiation* (Table 6.4.3-2). For example, assuming an ERR of 0.11, when the *Gateway Effect* is experienced by 50% of the *Additional Initiation* group, survival decreases by 210 individuals compared to *Additional Initiation* without any *Gateway Effect*. Compared to the positive benefit of *Switching*, the impact of the *Gateway Effect* is much smaller, suggesting that it can be counteracted by *Switching*; this is explored in tipping point analyses below.

6.4.3.1.4.9 Summary of Component analyses using empirically-derived inputs

The DPM(+1) modeler provides insight into the likely population impact of a Camel Snus MRTP and its proposed modified risk advertising. Relying primarily on empirically-derived estimates of tobacco use transitions as model inputs – both benefits and harms – this comprehensive model

projects that making Camel Snus available as an MRTP would increase survival by approximately 6,000 individuals in a single birth cohort of 1 million males.

Component analyses examining the effect of individual tobacco use transitions in isolation show that the dominant influence on the overall population health effects of a Camel Snus MRTP is from *Switching*. The effects of other transitions are comparatively much smaller, by an order of magnitude. The most impactful adverse transition is *Relapse* following *Diversion from Quitting*, that is, the effect if one presumes that half of the smokers who adopt Camel Snus instead of quitting are thereby caused to resume smoking. This hypothetical effect is estimated to reduce survival by 859 (assuming ERR=0.11); the favorable effect of *Switching* (after discounting for *Resumed Smoking)* is 7.5 times larger. The pattern of results obtained with modeling suggests that even low levels of *Switching* to Camel Snus instead of continuing to smoke are sufficient to overcome the adverse impact of harmful tobacco use transitions that might occur with an MRTP. This proposition is examined in the following section.

6.4.3.2 Tipping point analyses

Unlike the analyses using empirically-derived estimates of tobacco use transitions, which aim to estimate what are deemed to be realistic scenarios, tipping point analyses explore the boundaries of the model to determine where the model outputs project a tipping point between negative and positive population health effects. The analyses discussed above make clear that the biggest source of beneficial effects on population health (survival) is from *Switching* from smoking to Camel Snus (among smokers not likely to quit), which is the behavioral outcome intended by the proposed modified risk advertising for Camel Snus. Accordingly, tipping point analyses seek to determine how much *Switching* is necessary to offset the harmful effects of other tobacco use transitions. As the focus of tipping point analyses are specifically on the beneficial effect of *Switching*, the other beneficial transition in the model – *Alternative Initiation* – is not included in any tipping point analyses (and the effect of subsequent *Delayed Smoking*, which was to reduce those benefits, was, therefore, moot).

In this section, the tipping point is defined as the level of *Switching* that neutralizes the negative effects of the harmful tobacco use transitions in the model; that is, the level of *Switching* at which the net population effect is neutral, that is, near zero. (Other tipping point definitions are considered in the underlying modeling report Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report.) The Master model considers all of the harmful tobacco use transitions defined in Table 6.4.3-1 except *Relapse*, considering the level of *Switching* that would be necessary to overcome the effect of all of the posited harmful transitions. To further test the limits of the effects of *Switching*, several Component analyses use extreme estimates of particular harms. That is, they ask what percent of *Switching* would be necessary to offset even extreme and unrealistic estimates of certain potential harms.

6.4.3.2.1 Master model

6.4.3.2.1.1 Model specifications

The Master model incorporates empirically-derived estimates from the likelihood of use study for all of the harmful primary tobacco use transitions and conservative estimates for the secondary tobacco use transitions *Gateway Effect* and *Resumed Smoking*[9] to assess how much *Switching* is needed to offset these potential harms. The model uses the inputs shown in Table 6.4.3-1, with the exception that *Alternative Initiation*, a beneficial transition, is not included, in order to focus on the beneficial effects of *Switching*. *Gateway Effect* and *Resumed Smoking* are estimated at 50%. Based on the projected use rates from the likelihood of use study, *Diversion from Quitting* varies by age, generally declining from 20.0% to 1.8%. *Additional Initiation* is estimated at 0.3% for the 13-27 age intervals.

As discussed above, the model does not incorporate estimates of *Relapse*, as it cannot be accommodated in the integrated model. To assess the effects of *Relapse*, additional analyses were run in which the tipping point is considered to have been reached when the net positive effect on survival is sufficient to offset the negative effects of *Relapse*. In other words, the tipping point analyses require the effect of *Switching* to be sufficiently favorable to offset the effects of *Relapse*, which were estimated separately. Thus, these tipping point analyses assess how much *Switching* must occur to offset all potential harmful tobacco use transitions.

6.4.3.2.1.2 Model estimates

Incrementally increased rates of *Switching* were tested in these analyses (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report). It is informative to examine the estimates with 0% *Switching*, as this represents the cumulative effect of the posited harmful tobacco use transitions (*i.e.*, the deficit that *Switching* needs to overcome).

When no *Switching* and an ERR of 0.11 is assessed, the potential harm of Camel Snus and its proposed advertising as an MRTP is a reduction in survival estimated to be 733 fewer survivors. The tipping point for *Switching* is 0.47%. That means when 0.47% of smokers who would not otherwise quit smoking switch permanently to Camel Snus in each age interval of follow-up, the harmful effect of other tobacco use transitions is neutralized; that is, the difference in survivors between the counterfactual scenario and base case is 'near zero'. (Note that this does not provide for *Resumed Smoking*; *i.e.*, this is the percentage needed to switch persistently.) For an ERR of 0.08, the harmful tobacco use transitions result in the survival of 616 fewer individuals

[9] As noted above, the harmful secondary tobacco use transition of *Delayed Smoking,* whose effect is to reduce the benefit of *Alternative Initiation*, is not included. As the benefits of *Alternative Initiation,* which is the logical predicate to *Delayed Smoking*, are not included in tipping point analyses, the effect of *Delayed Smoking* cannot be included either.

to age 72. This deficit is overcome by persistent *Switching* at 0.38% in each age interval of follow-up.

Thus, these analyses indicate that if one takes realistic estimates of *Additional Initiation* and *Diversion from Quitting*, and conservative estimates of *Gateway Effect* and *Resumed Smoking*, and uses the conservative estimate of ERR at 0.11, having 0.47% *Switching* persistently to Camel Snus instead of continuing to smoke in each age interval is sufficient to offset any potential harmful tobacco use transitions that might occur.

As noted earlier, the integrated Master model does not incorporate the potential harmful effect of *Relapse*. However, the effect of *Relapse* was assessed separately, and the tipping points were re-estimated so as to offset *Relapse* effects. Assessing *Relapse* conservatively (*i.e.*, assuming 50% of the *Diversion from Quitting* group are caused to *Relapse* to smoking) increases the tipping point for *Switching* to 0.92% and 1.01%, for ERR = 0.08 and 0.11, respectively. In other words, roughly 1% of smokers *Switching* persistently to Camel Snus in each age interval of follow-up is sufficient to offset all the potential harmful tobacco use transitions possible with a Camel Snus MRTP.

6.4.3.2.1.3 Sensitivity testing for the value of the ERR

The DPM(+1) modeler incorporated two estimates of the ERR for Camel Snus compared to smoking – 0.08 and 0.11 – derived from expert consensus about these relative risks (Levy *et al*. 2004). These ERR values were modeled as having some uncertainty, which is incorporated in the PIs. To further explore how the value of the ERR affects the estimated population impact of a Camel Snus MRTP, additional sensitivity analyses were conducted using a variant of the tipping point approach. That is, the question of how high the ERR would need to be (*i.e.*, how small the risk-reduction between smoking and Camel Snus would have to be) to offset the expected population benefit of a Camel Snus MRTP was assessed.

The assessment of variations in the ERR used the same tobacco use transitions shown in Table 6.4.3-1. Under these input assumptions, a range of ERR values was assessed to identify the value of ERR at which the net population effect was near zero – *i.e.*, no benefit or harm. That value is when ERR=0.48, which means as long as the health effect of using Camel Snus is less than 48% of the risk of smoking, a Camel Snus MRTP is expected to have a positive effect on population health. This value of 0.48 is roughly 4 to 6 times higher than the expert consensus value for the ERR (0.08 or 0.11; Levy *et al*. 2004), indicating that there is very substantial headroom for a higher-than-estimated ERR that would still result in a Camel Snus MRTP producing a net benefit to population health. This lends confidence that a Camel Snus MRTP with modified risk advertising is likely to benefit population health.

6.4.3.2.2 Analyses examining extreme rates of harmful tobacco use transitions

To further explore the boundaries of the population effects from the introduction of Camel Snus with modified risk advertising, several analyses were run to examine the projected effects

if particular harmful tobacco use transitions are input at extreme values to determine the amount of *Switching* needed to counteract these posited extreme harms.

6.4.3.2.2.1 Impact of 50% rate for Diversion from Quitting

Specifications

This analysis explores the projected impact when 50% of smokers who were likely to quit are diverted from quitting. (This is in contrast to the empirical estimates for *Diversion from Quitting* from the likelihood of use studies, which range from 1.8% to 20% across ages, averaging about 5%.)

Analysis estimates

The analysis indicates that, with no *Switching* and an ERR of 0.11, the potential harm of a 50% proportion of *Diversion from Quitting* without any beneficial tobacco use transitions reduces survival by 2,002 in the cohort. The tipping point for *Switching* is 1.29% that is, if 1.29% of smokers in the base case who would not have quit smoking switch to Camel Snus, that harmful effect would be neutralized. For an ERR of 0.08, the posited 50% proportion of *Diversion from Quitting* without any beneficial tobacco use transitions results in survival of 1,477 fewer individuals in the cohort, but 0.90% of smokers *Switching* is sufficient to offset that harm.

Thus, these analyses indicate that if one assumes an extreme situation where half of all smokers in the base case who were going to quit smoking instead switch to Camel Snus, and using the conservative estimate of ERR at 0.11, having 1.29% *Switching* in each age interval of follow-up among smokers not intending to quit is sufficient to neutralize any potential harm.

6.4.3.2.2.2 Impact of Additional Initiation equal to the smoking initiation rate

Specifications

This analysis explores the projected impact if the likelihood of *Additional Initiation* due to a Camel Snus MRTP were to be as high as the likelihood of smoking initiation in the counterfactual case; that is, if Camel Snus attracts as many initiates as smoking attracts, but among youth otherwise not likely to smoke. Specifically, the analysis posits that 13.75% of 13-17-year-olds, 10% of 18-22-year-olds, and 1% of 23-27-year-olds who were not using any tobacco product, and who were not otherwise headed to smoking, would initiate with Camel Snus. (By comparison to these posited rates, which average 8.25% across these age intervals, the empirically-derived estimate for Camel Snus initiation is 0.3% in each of the age intervals.)

Analysis estimates

In the extreme situation where *Additional Initiation* is as common as smoking initiation and there are no beneficial tobacco use transitions, the model projects a reduction in survival of 5,557 individuals, assuming an ERR of 0.11. Tipping point analysis indicates that if *Switching* were 4.12%, or just over 4% of continuing smokers switched persistently to Camel Snus instead

of continuing to smoke, the harm from high rates of *Additional Initiation* would be offset. For an ERR of 0.08, the projected reduction in survival is 3,800, which would be completely offset by 2.60% of smokers *Switching* persistently to Camel Snus.

The tipping point analysis reveals that a persistent *Switching* rate of 2.60% (ERR=0.08) to 4.12% (ERR=0.11), across age intervals, would reverse the adverse effect of even these very extreme probabilities of *Additional Initiation*.

6.4.3.2.2.3 Impact of Additional Initiation at 10 times the empirical estimate with 50% Gateway Effect

Specifications

This analysis explores the projected impact if the rate of *Additional Initiation* is 10 times as great as what was estimated from the likelihood of use study Execution 1 (*i.e.*, 3% instead of the estimated 0.3%), 50% of those in the *Additional Initiation* group subsequently progress to smoking (*Gateway Effect*), and there are no countervailing beneficial tobacco use transitions.

Analysis estimates

In the extreme situation (*Additional Initiation* 10 times as great as predicted, 50% *Gateway Effect*, no opposing beneficial transitions and an ERR of 0.11), the model projects a reduction in survival of 4,049 individuals at age 72. The tipping point analysis indicates that 2.80% *Switching* persistently in each age interval of follow-up would be enough to counteract and neutralize this potential harm. For ERR=0.08, the projected reduction in survival is 3,720, which would be overcome by 2.43% of smokers *Switching* to Camel Snus in each age interval of follow-up.

The tipping point analysis reveals that if 2.43% (ERR=0.08) to 2.80% (ERR=0.11) of smokers who would not otherwise quit engaged in persistent *Switching* to Camel Snus in each age interval of follow-up, this would reverse the adverse effect of these extreme rates of *Additional Initiation* and *Gateway Effect*.

6.4.3.2.2.4 Summary of Tipping Point Analyses

The tipping point analyses assess the rates of *Switching* (switching persistently to Camel Snus instead of continued smoking, among smokers who were not headed towards quitting) that would be necessary to overcome potential harms – either all harmful tobacco use transitions or extreme counterfactuals (Component analyses). The DPM(+1) estimates that persistent *Switching* rates of about 1% in each age interval of follow-up are sufficient to ensure that the net population effect on mortality is not adverse in the face of all potential harms as estimated in the Master model (*i.e.*, empirically-derived estimates of harmful primary tobacco use transitions and conservative specifications for secondary tobacco use transitions, including *Relapse*). In analyses of hypothetical scenarios using very extreme values for harmful tobacco use transitions, a persistent *Switching* rate of about 4% in each age interval of follow-up is enough to counteract even these extreme hypothetical scenarios.

6.4.3.3 Scaling and extrapolation of the modeling to population-based cohorts

The analyses presented thus far are based on a hypothetical cohort consisting of 1 million males that is followed forward from age 13 to estimate survival at age 72. This section presents two extensions of the analyses. The first scales the results of the analyses to apply to a single cohort that is more realistic in size and gender balance. That is, the *results* are scaled from 1 million males to 4.1 million individuals (the actual size of a single U.S. birth cohort) of mixed gender. The second extrapolation expands the analyses from addressing a single birth cohort to addressing what the effect might be in each of the multiple cohorts that make up the full U.S. population aged 13-72. Each extension is discussed below.

6.4.3.3.1 Scaling the effects modeled for a cohort of 1 million males to a full cohort of mixed gender

The analyses presented thus far are based on a cohort of 1 million males, followed starting at age 13. In reality, there are 4.1 million 13-year-olds in the U.S. of whom 51% are female (U.S. Census Bureau 2016). Analyses suggested that, because the life table for females is different from the male life table, the benefit of the Camel Snus MRTP would be 19% lower for women[10] (*i.e.*, 81% that accruing to males) (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report, Appendix H). Accordingly, one can scale the effects on the entire mixed-gender cohort of 4.1 million[11] by multiplying the estimates from the 1 million-person male cohort by 3.70271 (4.1 {cohort scaling} * [0.49 {proportion male} +(0.51 {proportion female} * 0.81 {gender correction for mortality differential}]). This is expected to more realistically model population effects, as the true population is, of course, of mixed gender, and the empirically-derived estimates of tobacco use transitions were derived from a mixed-gender sample in the likelihood of use study. The resulting estimated effects on survival for this mixed-gender cohort are shown in Table 6.4.3-3.

As the scaling to a mixed-gender cohort is based on a multiplier applied to the figures in Table 6.4.3-2, the dynamics are identical, but the numbers are on a more realistic scale. Extension of the analyses to scale the Master model (with *Relapse*) results to this mixed-gender cohort indicates that a Camel Snus MRTP would increase survival by 18,000-20,000 lives. On its own, even allowing for 50% *Resumed Smoking*, *Switching* among smokers who would otherwise continue to smoke remains the biggest influence on survival, improving survival by approximately 24,000-25,000. Estimates of tipping points remain the same, as they are unaffected by this scaling.

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[10] The difference was 20% for ERR=0.08 with 50% *Relapse* (see Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 1, Final Report, Appendix H Table H7). For simplicity, 19% was used for all analyses.

[11] This mixed-gender cohort analysis, like the male-only cohort analyses, uses the transition probabilities derived from the likelihood of use study, which were based on a sample of mixed gender. Thus, neither the male-only nor mixed-gender analyses adjust for possible gender-based differences in tobacco use transition probabilities.

This extension of the analyses indicates that a Camel Snus MRTP is expected to have substantial beneficial effects on the population, increasing survival at age 72, by 18,000-20,000 in a single mixed-gender birth cohort of 4.1 million.

Table 6.4.3-3: Estimated changes in survival to age 72 in a single birth cohort of 4.1 million males and females, followed from age 13 to age 72

	ERR = 0.11			ERR = 0.08		
Model	**Estimated change in survival**	**95% Posterior Interval**		**Estimated change in survival**	**95% Posterior Interval**	
		Min	**Max**		**Min**	**Max**
Master model	21,294	18,491	24,156	22,942	19,987	25,975
Master model, with *Relapse* ♦	18,643			20,161		
Component analyses††						
Switching	43,929	38,690	49,216	46,195	40,696	51,731
Switching with *Resumed Smoking**	23,882	21,043	26,767	25,108	22,127	28,122
Diversion from Quitting	-1,177	-1,026	-1,340	-870	-755	-985
Diversion from Quitting with *Relapse** ♦	-4,358			-4,203		
Alternative Initiation	296	252	344	337	289	389
Alternative Initiation with *Delayed Smoking**	167	133	204	189	152	226
Additional Initiation	-759	-715	-803	-537	-496	-574
Additional Initiation with *Gateway Effect**	-1,537	-1,470	-1,611	-1,414	-1,348	-1,481

†† Refer to the tobacco use transitions in Table 6.4.3-1 where each tobacco use transition is described.

* Analyses that include secondary tobacco use transitions necessarily must also include their predicate primary transitions. The impact of the secondary transition can be estimated by the difference in survival between the model run with the secondary transition and the model run with only the predicate primary transition.

♦ The estimated change in survival in these model runs incorporates *Relapse* effects. As discussed in this section, *Relapse* in the same age interval cannot be fully incorporated into the DPM(+1), but its effects can be estimated by comparing two counterfactual scenarios. The reduction in projected survival due to *Relapse* is used to reduce the projected survival estimates in model runs that include *Relapse* compared to the same model run without *Relapse*. However, because the difference between the counterfactual scenario and the base case is not estimated directly for counterfactual scenarios incorporating *Relapse*, 95% PIs are not provided.

6.4.3.3.2 Extrapolating the effects modeled for a cohort of 1 million males to multiple cohorts in the current population

The Master model and Component analyses discussed above consider the effect of a Camel Snus MRTP only for single tobacco-naïve cohorts entering their teen years when a Camel Snus MRTP first becomes available. However, this focus on a single cohort does not consider the potential effect of the introduction of a Camel Snus MRTP on other cohorts, particularly those that are already past age 13, and that may also use a Camel Snus MRTP when it becomes available. Notably, it does not assess the potential benefit to people who are already smoking at the time the MRTP with modified risk advertising is introduced and could benefit from *Switching* completely to Camel Snus.

The DPM(+1) is designed to estimate the effect of an intervention on a single cohort that is followed over time to a certain end-point (in this case, from the age of tobacco initiation to age 72). Results from the DPM(+1) single cohort-based model runs were extrapolated to estimate effects in multiple cohorts representing the full population. The current population can be thought of as a series of birth cohorts, each of which has reached a different age at the time the Camel Snus MRTP becomes available. For these multiple cohort analyses, the introduction of the Camel Snus MRTP occurs at different ages for each birth cohort and affects current smokers in addition to never tobacco users. Thus, in aggregate, it aims to estimate the effect of introducing the MRTP to a population of mixed age (13-72 years) and smoking status. Consistent with the single-cohort analyses, the cohorts were grouped into 5-year age intervals, as shown in Table 6.4.3-4.

To assess the effect of introducing a Camel Snus MRTP into each cohort, the model posits that each age group reaches its index age with cigarettes available, but not a Camel Snus MRTP. Each age group then gains access to a Camel Snus MRTP at their "current" age – enabling transitions to Camel Snus as they enter the next 5-year age interval. (So, for example, individuals in the cohort now age 33-37 may initiate or quit smoking up to that age, and then may engage in *Switching* to Camel Snus starting at age 38.) The analyses are based on the estimated tobacco use transitions that make up the Master model (*i.e.*, representing empirically-estimated primary tobacco use transition probabilities and conservative estimates of secondary transitions (except for *Relapse*, which cannot be included in the Master model, as discussed previously). Separate analyses were run assuming an ERR=0.08 and 0.11.

This multiple cohort full population analysis applies the inputs used in the single-cohort analyses (*i.e.*, the 2000 mortality rates, the 2009 smoking initiation rates, the 2005-2008 smoking cessation rates) to multiple cohorts that may have different tobacco use and survival experiences. As such, this extrapolation should be taken only as a heuristic indication of the potential impact on these cohorts.

As in the single-cohort analyses, the modeling was based on a hypothetical cohort of 1 million males in each age interval. Table 6.4.3-4 shows the predicted effect on survival to age 72 for each of these 1 million male cohorts. The table shows that a Camel Snus MRTP would benefit

survival for individuals in each of the 5-year age intervals at the time the Camel Snus MRTP is introduced. The estimated magnitude of the benefit is greatest in the younger cohorts, which is expected since smokers in those age intervals have the shortest history of smoking, have the most time available to switch to Camel Snus, and gain the benefit from switching over a longer period of time. Indeed, in some of the older age intervals, many smokers will already have died before the Camel Snus MRTP is introduced. Thus, it is expected that younger individuals will reap the most benefit from the introduction of a Camel Snus MRTP. Conversely, though, the benefits accruing to older individuals are realized sooner, as they are closer to age 72 (the age at which survival is tallied in the model).

Table 6.4.3-4: Estimated change in survival[¶] to age 72 for multiple cohorts of 1 million males each, representing the profile of the current population, by age at the time of an MRTP introduction

Age at MRTP availability		ERR = 0.11			ERR = 0.08		
		Estimated change in survival	95% Posterior Interval		Estimated change in survival	95% Posterior Interval	
For initiation	For switching		Min	Max		Min	Max
13-17	18-22♦	5,751	4,994	6,524	6,196	5,398	7,015
18-22	18-22	5,903	5,154	6,669	6,332	5,542	7,144
23-27†	23-27	4,372	3,818	4,935	4,668	4,083	5,262
	28-32	2,880	2,514	3,259	3,063	2,677	3,462
	33-37	1,753	1,529	1,985	1,861	1,624	2,106
	38-42	972	847	1,104	1,034	902	1,173
	43-47	604	525	686	638	555	725
	48-52	276	239	314	291	253	331
	53-57	94	82	108	99	86	113
	58-62	42	36	48	44	38	50
	63-67*	10	9	11	10	9	12

[¶]Based on the tobacco use transitions in the Master model (Table 6.4.3-1) without *Relapse*. The estimates are for a cohort of 1 million males in each age interval.

♦ This cohort cannot engage in *Switching* until it has initiated smoking, which can occur in the 13-17 age interval at the earliest. Hence, the first age for *Switching* is later than the age for initiation.

† Initiation is modeled as ceasing after age 27.

* This is the last age interval during which *Switching* can make a difference in the outcome (survival).

The multiple cohorts of 1 million males each do not represent the size and gender composition of U.S. birth cohorts. To estimate results for a more representative population, the results from Table 6.4.3-4 are adjusted to include females and reflect differential mortality between males and females. For each age interval, differences in survivors shown in Table 6.4.3-4 are adjusted for differences in mortality (19% lower in females than in males) for the age at which the MRTP becomes available within each age interval. Table 6.4.3-5 shows the results for ERR=0.11 and ERR=0.08.

Table 6.4.3-5: Estimated changes in survival[¶] to age 72 for mixed-gender cohorts, sized to the U.S. population aged 13 to 67 at the time of the hypothetical Camel Snus MRTP introduction

Age at MRTP availability		ERR	
For initiation	For switching	0.11	0.08
13-17	18-22♦	107,289	115,336
18-22	18-22	91,591	98,053
23-27†	23-27	65,836	70,186
	28-32	41,157	43,742
	33-37	22,593	24,002
	38-42	12,051	12,785
	43-47	6,460	6,819
	48-52	3,001	3,163
	53-57	1,248	1,313
	58-62	501	520
	63-67*	89	89

[¶]Based on the tobacco use transitions in the Master model (Table 6.4.3-1) without *Relapse*.
♦ This cohort cannot engage in *Switching* until it has initiated smoking, which can occur in the 13-17 age interval at the earliest. Hence, the first age for *Switching* is later than the age for initiation.
† Initiation is modeled as ceasing after age 27.
* This is the last age interval during which *Switching* can make a difference in the outcome (survival).

These analyses suggest that a Camel Snus MRTP would increase survival for individuals in each age interval. Note that these estimates do not include the adverse effects of *Relapse*, which reduces the survival benefit by approximately 12% (Table 6.4.3-2 and Table 6.4.3-3).

While the figures from this full population extrapolation are not precise, together with the primary single-cohort model analyses, the multiple-cohort analysis further emphasizes the potential for a Camel Snus MRTP to provide substantial benefit to population health.

6.4.4 Limitations and Strengths

In advance of actual in-market experience with an MRTP, modeling provides a means of estimating the likely impact of product availability and use on population health. Like all modelers, the DPM(+1) modeler relies on simplifying assumptions about the dynamics of tobacco use and tobacco-related mortality. Importantly, wherever possible, model inputs were based on empirical data, and the model was validated against observed data on mortality in the U.S. (for smoking) and Sweden[12] (for snus use).

[12] This was done in a separate validation exercise (Bachand and Sulsky 2013). The modeling of Camel Snus MRTP effects did not use estimates from the Swedish population; it used U.S.-based smoking mortality statistics, and the specified ERR values to model the effects of snus on mortality, and U.S.-based likelihood of use data to model tobacco use transitions.

The DPM(+1) modeler estimated survival for a hypothetical male cohort of 1 million individuals and used smoking and mortality data for males as inputs. Extrapolating the model to project effects for a single mixed-gender cohort of males and females is based on analyses that estimate the effect on females to be 19% lower than for males. Input probabilities for tobacco use transitions were not differentiated by gender: the empirically-derived probabilities of primary tobacco use transitions are based on data from the entire mixed-gender sample included in the likelihood of use study, and the arbitrary or extreme inputs for secondary tobacco use transitions also are not gender-specific.

Extrapolation of the single-cohort analyses to estimate the effects on the multiple cohorts that make up the current population implicitly assumes that the inputs (smoking and mortality data, tobacco use transition probabilities) will not vary across age cohorts. It is likely that these parameters do vary. Nevertheless, the analysis provides some insight into the scale of the potential benefit of a Camel Snus MRTP on the different cohorts that make up the current U.S. population aged 13-67.

Many inputs to the DPM(+1) model are taken from results of the likelihood of use study, which assessed the interest of various subgroups in purchasing Camel Snus for personal trial. Self-reported purchase intent ratings from the likelihood of use study were translated into purchase probabilities (as a proxy for likelihood of use) using an empirically-validated algorithm. It is likely that these projections over-estimate the adoption of Camel Snus. However, the overestimation is likely to apply across the board, and an overall reduction in the use of Camel Snus reduces both benefits and harms, since both depend on use of Camel Snus, just by different subsets of the cohort (*i.e.*, smokers versus non-smokers). Thus, an overall change in the estimated appeal of Camel Snus is unlikely to change the conclusion that the net effects of an MRTP are positive. Indeed, the DPM(+1) model results show that even reducing all of the estimated transition probabilities by 75% (*i.e.*, simulating an across-the-board decrease in use of Camel Snus) does not change the fundamental conclusion that a Camel Snus MRTP would result in a net benefit to population health.

In another respect, using estimates of use based on the likelihood of use study may underestimate use of Camel Snus. The results of the likelihood of use study are based on a single exposure to a tobacco company advertisement. Repeated exposures may increase interest in a modified risk tobacco product. This mode of communication may also have limited impact because consumers are skeptical of claims made in advertisements and are particularly suspicious of claims made by a tobacco company (Harris Interactive 2013; Byrne *et al*. 2012). Accurate information about reduced risk of Camel Snus compared to smoking from other, more authoritative, sources may increase the appeal of a modified risk tobacco product, particularly to current smokers not interested in quitting.

The modeling results presented here benefit from considerable strengths. The DPM(+1) considers multiple tobacco use transitions that could affect population health. The DPM(+1) modeler itself and the empirical inputs regarding tobacco use and its effects on survival were

validated against population data for smoking (in the U.S.) and snus use (in Sweden)[13]. The DPM(+1) considers the uncertainty around certain parameters and produces PIs that reflect that uncertainty. The model makes conservative assumptions – for example, by not including the benefits of quitting Camel Snus – suggesting that the benefits may be greater than estimated. The results present only the impact on a single cohort of individuals coming into the age of risk for tobacco initiation. Extrapolations of the model results that consider potential effects on the full population, including those who are already smoking, suggest that the beneficial effects of a Camel Snus MRTP would actually be realized by individuals in all age intervals.

6.4.5 Summary

The DPM(+1), a validated modeler for estimating tobacco-related mortality in a population, was used to assess a diverse set of hypothetical scenarios to consider a spectrum of potential benefits and harms from a Camel Snus MRTP order. The DPM(+1) modeler considers primary tobacco use transitions based on estimates empirically-derived from the likelihood of use study, as well as non-empirical estimates of secondary tobacco use transitions that are considered to be conservative. The Master model considers all of the benefits and harms (with separate adjustment for *Relapse*), while Component analyses estimate the effects of particular tobacco use transitions that are sources of benefit or harm. Besides evaluating scenarios considered to be realistic, tipping point analyses evaluate what percentage of current smokers who were not likely to quit – the intended population for a Camel Snus MRTP – would need to switch persistently to Camel Snus (*Switching*) in each 5-year age interval in order to overcome various conservatively-estimated harms to yield a net positive impact on population health (survival).

Model outcomes are expressed as incremental survival of a single U.S. birth cohort comprised of one million individuals who were 13 years of age at the time of MRTP availability. Following a single cohort that enters the age of tobacco initiation at a time when a Camel Snus MRTP with modified risk advertising is (hypothetically) available yields valid estimates of the effects on that cohort. However, it underestimates the total benefit on the U.S. population, because it does not take into account the potential benefit to individuals already 18 or older at the time of a Camel Snus MRTP introduction, many of whom are already smoking, and thus stand to benefit from *Switching* to Camel Snus. Extrapolations estimate the effect of a Camel Snus MRTP order on the full population aged 13-67, for which a Camel Snus MRTP only becomes available at their current age. Although this exercise is less precise, it is important to consider this potential effect. Accordingly, it is important to consider the total population benefit, counting both a tobacco naïve cohort from age 13 as well as the multiple cohorts that constitute the current U.S. population aged 18 and older, which includes many adult smokers.

[13] This was done in a separate validation exercise (Bachand and Sulsky 2013). The modeling of Camel Snus MRTP effects did not use estimates from the Swedish population; it used U.S.-based smoking mortality statistics, and the specified ERR values to model the effects of snus on mortality, and U.S.-based likelihood of use data to model tobacco use transitions.

6.4.5.1 Net effects on population health (survival) are likely to be positive and unlikely to be negative

The modeling results consistently indicate that Camel Snus is likely to have a net positive benefit on population health, increasing survival for the population as a whole (*i.e.*, decreasing tobacco-related mortality). The Master model, including empirically-derived estimates of primary tobacco use transitions based on the likelihood of use study and employing a conservative ERR of 0.11, indicates that making a Camel Snus MRTP available with modified risk advertising would increase survival to age 72 by nearly 6,000 persons in a single birth cohort of 1 million males that enters its teenage years as the Camel Snus MRTP with modified risk advertising becomes available. Scaling the results to a mixed-gender cohort of 4.1 million individuals indicates that a Camel Snus MRTP would increase survival to age 72 by 18,000-20,000 individuals. Considering the full population, which includes adults who are presently smoking, the introduction of the Camel Snus MRTP is estimated to increase survival for individuals in each age interval.

Tipping point analyses using empirically-based estimates of all the potential harmful tobacco use transitions with a Camel Snus MRTP indicate that Camel Snus would offset projected harms if only approximately 1% of the intended user population (*i.e.*, current smokers who are not likely to quit) switched completely and persistently to Camel Snus in each age interval of follow-up. This suggests that having Camel Snus available with MRTP advertising will likely produce a population health benefit, and, moreover, that net population harm is unlikely.

The model uses estimates of the risk reduction due to *Switching* from smoking to Camel Snus that were based on expert estimates. Two estimates were used in these analyses – a 92% reduction in risk (ERR=0.08) and an 89% reduction (ERR=0.11) – and both were modeled with uncertainty. Additionally, a sensitivity analysis using the assumptions included in the Master model, considering all harmful and beneficial tobacco use transitions (after adjustment for *Relapse*), shows that the break-even point where the population is neither benefitted nor harmed, was an ERR of 0.48, or a reduction in risk compared to smoking of 52%. Therefore, even if *Switching* from cigarette smoking to Camel Snus only reduces risk by as little as 50% – much less than the expert estimates of 89%-92% – a Camel Snus MRTP would still have favorable effects on population health.

6.4.5.2 Influence of model inputs on estimated survival

The DPM(+1) outputs demonstrate that the biggest influence on population health and survival is *Switching* – that is, current smokers not likely to quit *Switching* to Camel Snus rather than continuing to smoke. All other tobacco use transitions considered in the model are dwarfed by the beneficial effect of this transition in tobacco use. For example, on its own (without other transitions or harms) empirically-derived rates of *Switching* from the likelihood of use study, applied over the life of the cohort, are estimated to yield an increase in survival of about 44,000-46,000 persons in the 13-year-old mixed-gender birth cohort. In contrast, estimating *Gateway Effect* even as high as 50% (among those who initiated Camel Snus and would not otherwise have used tobacco) results in a net loss to survival of about 1,500 in the birth cohort.

Clearly, the *Gateway Effect* has an adverse impact on population health, and steps should be taken to discourage initiation with Camel Snus and further progression to smoking. The modeling results indicate, however, that at the population level, the positive effect of *Switching* is much greater, and the net effect of Camel Snus availability is positive, even in the face of a *Gateway Effect*.

The reasons *Switching* has such a dominant effect on population health is that there are many smokers who are not likely to quit, this large group showed some of the greatest likelihood of using Camel Snus when presented with modified risk advertising in the likelihood of use study, and continuing smokers have multiple opportunities to engage in *Switching* over their lifetime. Further, the smokers who do switch to Camel Snus stand to gain very significant health benefits, reducing their mortality risk by 89-92% compared to smoking (Levy *et al*. 2004). These factors, in combination, yield very large population health benefits. In contrast, many of the adverse or harmful tobacco use transitions that raise concern about an MRTP apply to much smaller populations and/or to populations that were assessed in the likelihood of use study to have very low likelihood of using Camel Snus. Take *Gateway Effect* as an example. *Gateway Effect* occurs in non-tobacco users who would not otherwise have smoked but take up Camel Snus (the *Additional Initiation* group). The likelihood of use study results indicate that individuals who are not susceptible to smoking also have little interest in trying Camel Snus, suggesting that few of these individuals would adopt Camel Snus. That is why estimating *Gateway Effect* even as high as 50% does not result in large changes in population impact. The same logic applies to beneficial tobacco use transitions such as *Alternative Initiation*, which also occur infrequently, and therefore have minimal impact on net population health.

Parallel analyses were run with two literature-based estimates of risk reduction, an ERR of 0.08 and a more conservative ERR of 0.11. This change made only a modest difference in the estimated population health impact, suggesting that the conclusion that there is a population health benefit does not rest heavily on the precision of the ERR estimate. The modeler also considers the estimates of ERR to be uncertain, and that uncertainty is reflected in the 95% PIs cited in the tables. While the resulting PIs clearly reflect some uncertainty about the magnitude of the benefit of an MRTP for Camel Snus, they do not change the conclusion that there is a benefit. For example, in the Master model using empirically-derived estimates from the likelihood of use study and an ERR of 0.11, the point estimate is 21,294 additional survivors, and the lower bound of the PI is 18,491 survivors per cohort (Table 6.4.3-3) – both reflecting a very substantial population health benefit.

6.4.5.3 Tipping points

Given that *Switching* persistently to Camel Snus is the dominant beneficial tobacco use transition influencing the outcome of the statistical modeling and is the behavior the proposed modified-risk advertisement promotes, tipping point analyses were conducted to assess how much *Switching* is necessary to produce a neutral or beneficial population health impact in the face of extreme estimates of harmful tobacco use transitions. In a Master model using empirically-derived estimates for all primary harmful tobacco use transitions, except *Relapse*,

and not including any other beneficial tobacco use transitions, approximately 1% *Switching*, in each age interval of follow-up, is enough to neutralize the potential harmful tobacco use transitions. Estimates based on the likelihood of use study project trial of Camel Snus to be at least this proportion even in the oldest age interval that would benefit from *Switching* and within which the beneficial effect of *Switching* is smallest. As a further context for the 1% rate of *Switching* needed to overcome all the posited harms, the projected *Switching* proportions in the two youngest age intervals where *Switching* could occur (18-22, 23-27), and where *Switching* confers the greatest health benefit, are at least 5 times as great as the *Switching* rate required at the tipping point. Thus, tipping point analyses suggest that achievable rates of *Switching* from smoking to Camel Snus can produce a net benefit in population health (survival).

6.4.5.4 Conclusion: Net population health effects of a Camel Snus MRTP with modified risk advertising are likely to be positive and unlikely to be negative

Modeling the effects with empirically-derived estimates of tobacco use transitions indicate a likely increase of 18,000-20,000 survivors to age 72 for a mixed-gender single birth cohort comprised of non-tobacco-users at age 13. The biggest influence on the net population impact is the proportion of smokers *Switching* to Camel Snus instead of continuing to smoke, reducing their health risks. Even in tipping point analyses that make strongly negative assumptions about rates of harmful tobacco use transitions, a rate of *Switching* of less than 3% in each age interval of follow-up would neutralize these extreme rates of harmful tobacco use transitions. Moreover, tipping point analyses using more realistic empirically-based estimates of rates of harmful tobacco use transitions based on the likelihood of use study indicate no population harm even if only 1% *Switching* occurs in each age interval of follow-up. Sensitivity analyses for the risk reduction between Camel Snus and smoking show that a Camel Snus MRTP with modified risk advertising would likely produce a population health benefit even if the risk reduction were only about 50%, rather than the approximately 90% estimated by experts (Levy *et al*. 2004). Thus, extensive modeling of the likely impact of a Camel Snus MRTP demonstrates that marketing of Camel Snus with modified risk advertising is likely to produce a net benefit to population health and is unlikely to result in net negative effects on population health (survival).

6.4.6 Modeling Results for Execution 2

The proposed modified risk advertisement presented in Execution 2 included claims for significantly reduced risk of lung cancer, oral cancer, respiratory disease, and heart disease for smokers who switched completely from using cigarettes to Camel Snus. This section provides results of the modeling conducted for Execution 2 (complete statistical modeling results for Execution 2 are in Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report). To assess the likely impact of the advertising presented in Execution 2, the DPM(+1) modeler uses the estimates of Camel Snus use from the likelihood of use study Execution 2, as described below.

6.4.6.1 Model using empirically-derived estimates

6.4.6.1.1 Modeler inputs

The DPM(+1) modeler uses empirically-derived estimates as inputs for the probability of all primary tobacco use transitions, based on results of the likelihood of use study Execution 2 (Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Second Execution of Consumer Testing* – Amended Final Report). Individuals with varying tobacco use status were shown the proposed Camel Snus MRTP advertising and rated their interest in trying Camel Snus (likelihood of purchase for trial). These ratings were converted into likelihood of use probabilities (*i.e.*, likelihood of purchase), which formed the basis for the empirical estimates of primary tobacco use transitions. Table 6.4.6-1 below shows the inputs to the model. *Switching* is posited to range from 16.0% to 2.0%, generally decreasing with age (see Table 6.4.6-1 below and Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Second Execution of Consumer Testing* – Amended Final Report); *Diversion from Quitting* similarly varies by age, from 22.1% to 1.8%, generally decreasing by age. *Additional Initiation* is estimated at 0.3%, and *Alternative Initiation* at 0.85% for the 13-27 age intervals, based on the empirically-derived projections from the likelihood of use study among respondents ages 18-27 years. Secondary tobacco use transitions (*Gateway Effect, Delayed Smoking, Resumed Smoking,* and *Relapse*) cannot be projected from the likelihood of use study, and are thus included in the analyses as hypothetical (and in many instances, extreme) estimates, with a 50% probability of occurring.

6.4.6.1.2 Summary of results, Execution 2

Using the inputs in Table 6.4.6-1, which incorporate the findings of the likelihood of use study for Execution 2, a series of analyses were run. The results or outputs of the analyses are summarized in Table 6.4.6-2, which shows the estimated effect on survival at age 72 for a hypothetical cohort of one million males[14]. The entries represent the difference in survival between the counterfactual scenario (where some portion of the population uses Camel Snus as an MRTP) and the base case (where only cigarette smoking is an available tobacco use option). Positive numbers indicate improved survival and a benefit to population health in the counterfactual scenario; negative numbers indicate reduced survival and harm to population health. Also shown are the 95% Posterior Intervals (PI), which take into account the uncertainty posited for the input estimates to the base case model, as well as the estimated ERR for Camel Snus. Table 6.4.6-2 shows separate estimates, assuming an ERR of 0.11 and 0.08. Each row represents a set of model inputs, starting with the Master model, which includes almost all the transitions shown in Table 6.4.6-1, followed by Component analyses that isolate particular tobacco use transitions in order to provide insight on the impact of each transition. Primary tobacco use transitions are considered singly. Secondary tobacco use transitions are considered

[14] The DPM(+1) modeler is run on a hypothetical population of 1 million males. Since U.S. birth cohorts are actually about 4.1 million, 51% of whom are female (U.S. Census Bureau 2016), survival estimates are also provided for this more representative mixed-gender birth cohort.

together with their predicate primary transitions. For example, *Gateway Effect* (a secondary transition) can only occur after *Additional Initiation* (a primary transition). Therefore, one analysis considers *Additional Initiation* on its own, and another analysis adds *Gateway Effect*, whose individual contribution can be estimated as the difference between the two analyses. Each analysis is discussed briefly, with reference to Table 6.4.6-1 and Table 6.4.6-2.

Table 6.4.6-1: DPM(+1) inputs for the probability of tobacco use transitions, Execution 2

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact: Benefit or Harm	Modeled Probability	
Primary	Initiation with Camel Snus (instead of abstinence) by never users of tobacco who were *not* likely to initiate smoking	*Additional Initiation*	Harm	0.3%[a]	
Secondary	--- Subsequent progression to smoking due to use of Camel Snus	*Gateway Effect*	Harm	50%[d]	
Primary	Initiation with Camel Snus (instead of smoking) by never users of tobacco who *were* otherwise likely to initiate smoking	*Alternative Initiation*	Benefit	0.85%[a]	
Secondary	--- Subsequent initiation of smoking	*Delayed Smoking*	Harm†	50%[d]	
Primary	Adoption of Camel Snus (instead of smoking) by smokers who were *not* likely to quit	*Switching*	Benefit	**Age Interval**	**% Switching to Camel Snus**
				18-22	13.4
				23-27	12.9
				28-32	16.0
				33-37	9.1
				38-42	7.3
				43-47	6.5
				48-52	5.9
				53-57	3.3
				58-62	2.6
				63-67	2.8
				68+	2.0
Secondary	--- Subsequent return to smoking♦	*Resumed Smoking*	Harm†	50%[b]	

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact: Benefit or Harm	Modeled Probability	
				Age Interval	% Using Camel Snus
Primary	Adoption of Camel Snus by smokers who were likely to quit, who either switch to Camel Snus instead of quitting[¶] or who quit, then adopt Camel Snus*	*Diversion from Quitting*	Harm	18-22	15.4
				23-27	22.1
				28-32	13.6
				33-37	11.3
				38-42	11.3
				43-47	5.4
				48-52	7.1
				53-57	5.6
				58-62	2.6
				63-67	1.8
				68+	2.2
Secondary	--- Subsequent relapse to smoking**	*Relapse*	Harm	50%[c]	

--- Indicates a secondary transition among the population undergoing the primary transition immediately above.

† This secondary transition is not net-harmful but rather reduces the benefit of the prior primary transition. For example, if a certain proportion of smokers *Switching* quickly go back to smoking (*Resumed Smoking*), this negates the benefit of *Switching* for that subset, yet they are no worse off than they were before trying Camel Snus.

♦These analyses treat smokers who initially switch to Camel Snus but then return to smoking as though they never use Camel Snus at all, rendering this secondary tobacco use transition neutral in effect (the affected individuals were smoking before the transition and are smoking after the transition). That is, a return to smoking was treated as a reversal of *Switching*, discounting the estimated *Switching* rate. This is conservative, as it does not consider any benefit due to a limited period of use of Camel Snus versus continued smoking.

¶ These analyses do not consider the potential that adoption of Camel Snus might delay rather than completely deter smoking cessation. This is conservative, as it does not count any health benefit that would come from smoking cessation, even if cessation were delayed.

* Smokers who quit and then adopt Camel Snus are modeled as never having quit smoking, with no health benefit attributed to quitting. In essence, these analyses assume these smokers never quit, but adopt Camel Snus instead of quitting.

** The modeler cannot directly accommodate individuals who quit, adopt Camel Snus, and then *Relapse* to smoking within the same age interval. To model *Relapse*, the model was run with the likelihood of quitting reduced, which has roughly the same effect as having a certain proportion of quitters instead

continuing to smoke. This is conservative, as it does not account for any benefit of a period of smoking abstinence or use of Camel Snus. To discern the impact of *Relapse*, survival in in the counterfactual scenario of this run of the model is compared to survival in in the counterfactual scenario of a corresponding run of the model that does not include this effect. The difference in estimates between these two runs of the model is then used to adjust the estimated survival in analyses meant to include the *Relapse* effect.

[a] Applies only to ages 13-27
[b] Not empirically-derived; conservative estimate; reverses percentage of *Switching*
[c] Analyzed separately from other tobacco use transitions with results used to adjust projected survival; transition is not included in the Master model
[d] Applies only to ages 18-32; not empirically-derived; conservative estimate

Table 6.4.6-2: Estimated changes in survival to age 72 in a hypothetical cohort of one million males, followed from age 13 to age 72

	ERR = 0.11			ERR = 0.08		
Model	**Estimated change in survival**	**95% Posterior Interval**		**Estimated change in survival**	**95% Posterior Interval**	
		Min	**Max**		**Min**	**Max**
Master model	6,819	5,919	7,743	7,374	6,416	8,346
Master model, with *Relapse* ♦	5,675			6,175		
Component analyses††						
Switching	13,925	12,261	15,611	14,639	12,892	16,396
Switching with *Resumed Smoking**	7,702	6,779	8,630	8,093	7,127	9,063
Diversion from Quitting	-529	-463	-597	-390	-341	-440
Diversion from Quitting with *Relapse** ♦	-1,964			-1,892		
Alternative Initiation	136	116	158	155	132	178
Alternative Initiation with *Delayed Smoking**	77	61	94	87	70	105
Additional Initiation	-205	-193	-217	-145	-134	-155
Additional Initiation with *Gateway Effect**	-415	-397	-435	-382	-364	-400

†† Refer to the tobacco use transitions in Table 6.4.6-1 where each tobacco use transition is described.

* Analyses that include secondary tobacco use transitions necessarily must also include their predicate primary transitions. The impact of the secondary transition can be estimated by the difference in survival between the model run with the secondary transition and the model run with only the predicate primary transition.

♦ The estimated change in survival in these model runs incorporates *Relapse* effects. As discussed in this section, *Relapse* in the same age interval cannot be fully incorporated into the DPM(+1), but its effects can be estimated by comparing two counterfactual scenarios. The reduction in projected survival due to *Relapse* is used to reduce the projected survival estimates in model runs that include *Relapse* compared to the same model run without *Relapse*. However, because the difference between the counterfactual scenario and the base case is not estimated directly for counterfactual scenarios incorporating *Relapse*, 95% PIs are not provided.

6.4.6.1.3 Master model

6.4.6.1.3.1 Model specifications

The Master model incorporates all tobacco use transitions shown in Table 6.4.6-1, using the estimates of primary beneficial and harmful transitions derived from the likelihood of use study for Execution 2, and hypothetical (and in most instances, extreme) probabilities for secondary harmful transitions. Only *Relapse* (which separate analysis confirmed has relatively small effect) is omitted. Thus, this Master model incorporates all but one (*Relapse*) of the inputs defined in Table 6.4.6-1 and uses empirically-derived estimates from the likelihood of use study Execution 2 for all primary tobacco use transitions.

6.4.6.1.3.2 Model estimates

Table 6.4.6-2 shows the survival predictions from the Master model, which is run on a hypothetical cohort of one million 13-year-old males.

Master Model. This model includes all harmful and beneficial tobacco use transitions, with the exception of *Relapse* in the same age interval, which cannot be integrated into the model. Using the more conservative ERR of 0.11, the model projects a benefit of 6,819 additional survivors [95% PI: 5,919 to 7,743] at age 72 for the counterfactual scenario (Camel Snus MRTP available) versus base case (cigarettes only available). Using an ERR of 0.08 yields slightly more favorable results, with an estimated 7,374 survivors [95% PI: 6,416 to 8,346] – that is, 506, or 8.0% more survivors to age 72 than the model with the ERR of 0.11.

Master Model with Relapse. Although *Relapse* in the same age interval cannot be integrated into the Master model, the resulting estimate can be adjusted for *Relapse* effects, which are assessed separately. The *Relapse* adjustment reduces the estimated net survival to 5,675 for an ERR=0.11 and to 6,175 for an ERR=0.08.

Therefore, analyses that incorporate all primary harmful tobacco use transitions (based on empirically-derived estimates) and all harmful secondary transitions (based on hypothetical, and, in many instances, extreme, estimates) project the Camel Snus MRTP to result in substantial benefit to population health with approximately 6,000 additional survivors in a single birth cohort.

6.4.6.1.3.3 Sensitivity testing for the empirically-based estimates of transitions to Camel Snus

In the Master model, estimates empirically-derived from the likelihood of use study are used as assumptions about the probability of primary tobacco use transitions. These projections are based on self-reported interest in trying Camel Snus given by the study participants that are then applied to an empirical algorithm to estimate the probability of purchase for trial (New Tobacco Product 'Likelihood' Study: An Algorithm to Predict Usage of New Tobacco Products Prior to Market Launch – Methodological Report). Tests of the predictive algorithm indicated

that these projections may over-estimate the actual rate of transitions to use of Camel Snus. However, logically, consistently overestimating use of Camel Snus is not expected to change the conclusion that Camel Snus has a net positive effect on population health (survival), although it would be expected to change the magnitude of the benefit. The reasoning for this rests on the notion that adoption of Camel Snus is responsible for ***both*** the harms and the benefits in the model, with harms or benefits accruing depending on the population in question. So, if adoption of Camel Snus is lower than estimated, across the board, this would likely reduce both the benefits and harms proportionately, leaving unchanged the conclusion that a Camel Snus MRTP yields a population benefit, though reducing the magnitude of the benefit.

Therefore, a variation of the Master model was run in which all of the empirically-derived estimates of primary tobacco use transitions were reduced by 75%, while secondary transitions retained their original probabilities. As expected, that model run also yielded a net population benefit, with the magnitude of the benefit reduced by approximately 73% (1,998 additional survivors based on ERR=0.08, and 1,848 based on ERR=0.11). Thus, the conclusion that a Camel Snus MRTP is likely to benefit population health is robust to even extreme variations in the estimated appeal of Camel Snus, if, in fact, those variations are proportional.

6.4.6.1.4 Examining the contributions of different tobacco use transitions: Component analyses

The Master model assesses the joint effects of multiple tobacco use transitions on projected survival. The Component analyses that follow isolate the influence of specific components on survival. Thus, they do not represent, nor are they intended to represent, realistic scenarios but rather are included to provide conceptual insight into how the Master model inputs, considered in isolation, exert their influence on the model's outputs.

It should be noted that the effect of various components is not independent or additive; that is, one cannot simply sum the effects of all the components and derive the effects seen in the Master model. The different component parameters affect one another. For example, if *Additional Initiation* or *Alternative Initiation* increases, this results in fewer smokers in the next age interval, which in turn moderates the effect of subsequent transitions such as *Switching*.

6.4.6.1.4.1 Switching

Specifications

This Component analysis isolates the effect of *Switching*; that is, the effect of smokers who were not likely to quit smoking who switch completely to Camel Snus. This tobacco use transition confers a health benefit, because these individuals reduce their risk relative to continued smoking. *Switching* is estimated based on the likelihood of use study, which estimated the uptake of Camel Snus among smokers who were not likely to quit. The estimated rates of *Switching* decline with age and are assessed in an age-specific way.

Analysis estimates

As shown in Table 6.4.6-2, using the more conservative ERR of 0.11, *Switching* projects a survival benefit of 13,925 [95% PI: 12,261 to 15,611] additional survivors in the birth cohort. Using an ERR of 0.08 yields more favorable results with a projected 14,639 additional survivors [95% PI: 12,892 to 16,396] – approximately 700 more than when the ERR is 0.11 (an increase of 5%).

This analysis estimates the effect of smokers who were not likely to quit smoking who instead switch to Camel Snus, which substantially reduces their health risks. The estimated 14,000-person increase in survival is far greater than the figures estimated in the Master model that included many other tobacco use transitions, both beneficial and harmful. These analyses indicate that the effect of *Switching* is by far the tobacco use transition most affecting the population impact of a Camel Snus MRTP. (Accordingly, it is the focus of tipping point analyses presented subsequently.)

6.4.6.1.4.2 Resumed Smoking

Specifications

This Component analysis considered that some of the smokers not likely to quit who switch to Camel Snus instead of smoking would soon return to smoking. This secondary tobacco use transition would reduce the beneficial population impact of *Switching*. As this secondary tobacco use transition cannot be estimated from the likelihood of use data, it is assigned a probability of occurrence of 50% (*i.e.*, the impact of *Resumed Smoking* is estimated by reducing the empirically-derived estimate of *Switching* by 50%).

Analysis estimates

Table 6.4.6-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, a survival benefit of 7,702 [95% PI: 6,779 to 8,630] additional survivors is projected. Using an ERR of 0.08 yields more favorable results with a projected 8,093 additional survivors [95% PI: 7,127 to 9,063] – approximately 390 more than when the ERR is 0.11 (an increase of 5%).

Assuming that 50% of those *Switching* to Camel Snus quickly return to smoking reduces the projected survival benefit by almost half. (The reduction is slightly less than half because positing that half of those *Switching* return to smoking increases the pool of smokers who can subsequently quit smoking, whereas the model does not incorporate quitting of Camel Snus.) Nevertheless, *Switching*, even with *Resumed Smoking*, is estimated to improve survival to age 72 by at least 7,700 persons in the cohort.

6.4.6.1.4.3 Diversion from Quitting

Specifications

This Component analysis isolates the effect of *Diversion from Quitting*, which can be thought of as two potential mechanisms for harm – smokers who otherwise were expected to quit adopt Camel Snus instead of quitting, and smokers who actually do quit and then adopt Camel Snus instead of remaining tobacco free. In both cases, the result is assessed as harmful because Camel Snus carries more risk than abstinence from all tobacco use. Analyses do not distinguish between these two harms because of the assumption that any abstinence in these groups is short-lived and provides no health benefit.

The estimated rates of *Diversion from Quitting* are based on the likelihood of use study, which estimated uptake of Camel Snus among current smokers who were likely to quit. The estimates generally decline with age. Using only estimates from current smokers likely to quit is conservative because estimated rates of Camel Snus adoption among former smokers are much lower in the likelihood of use study (Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Second Execution of Consumer Testing* – Amended Final Report).

Analysis estimates

Table 6.4.6-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a deficit of 529 [95% PI: -463 to -597] fewer survivors. Using an ERR of 0.08 yields more favorable results with a projected 390 fewer survivors [95% PI: -341 to -440] – 220 more survivors than when the ERR is 0.11.

This analysis estimates the effect of taking up Camel Snus among smokers who were likely to quit smoking, which increases their risk compared to abstaining from all tobacco. The estimated reduction in survival is far smaller than the estimated increase in survival due to *Switching* among smokers who were not likely to quit (Table 6.4.6-2) because the increase in risk going from abstinence to use of Camel Snus is much smaller than the decrease in risk going from smoking to using Camel Snus. Furthermore, based on the results of the likelihood of use study, more smokers fall into the not-likely-to-quit group, and smokers who were likely to quit were less likely to adopt Camel Snus. This suggests that the increased survival due to *Switching* will overcome the harm due to *Diversion from Quitting* to yield a population benefit.

6.4.6.1.4.4 Relapse

Specifications

This Component analysis considers that some of the individuals in the *Diversion from Quitting* group – smokers who were expected to (or did) quit but adopted Camel Snus instead of complete abstinence from all tobacco – might resume smoking (*Relapse*). Individuals who *Relapse* would be substantially harmed because they incur the harms of smoking, which they

otherwise would have avoided but for their use of the MRTP. As described above, the impact of *Relapse*, estimated in a separate analysis, is used to adjust the estimated survival in the *Diversion from Quitting* analysis.

Because the probability of the secondary tobacco use transition of *Relapse* cannot be estimated empirically from the likelihood of use data, analyses include a conservative estimate of 50% of the *Diversion from Quitting* group who would *Relapse* to smoking.

Analysis estimates

Table 6.4.6-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11 and a very conservative estimate of *Relapse* at 50%, the projected survival is a deficit of 1,964 fewer survivors. The estimate (-1,892) is more favorable when the ERR is 0.08. Posterior Intervals cannot be computed for these *Relapse*-adjusted analyses.

These analyses show that, as expected, *Relapse* exacerbates the harm of *Diversion from Quitting*. For example, assuming an ERR of 0.11, *Relapse* decreases survival by 1,435 individuals in the cohort, compared to *Diversion from Quitting* without *Relapse*. This adverse effect is substantial. That it is substantially smaller than the expected beneficial effect of *Switching* suggests that it can be counteracted by sufficient *Switching* among smokers; this will be explored in the tipping point analyses below.

6.4.6.1.4.5 Alternative Initiation

Specifications

This Component analysis isolates the effect of *Alternative Initiation* (uptake of Camel Snus among non-tobacco users aged 13-27 who were otherwise expected to take up smoking). This tobacco use transition confers a benefit because these individuals avoid the excess risk of smoking. *Alternative Initiation* is estimated from the likelihood of use study in which non-tobacco-using respondents who were assessed as susceptible to smoking estimated their likelihood to take up Camel Snus. Based on extensive documented evidence of tobacco initiation by age in the U.S. population, initiation was limited to ages 13-27, and *Alternative Initiation* is estimated at 0.85% within each of the three 5-year age intervals covering this age range.

Analysis estimates

Table 6.4.6-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a benefit of 136 [95% PI: 116 to 158] additional survivors. Using an ERR of 0.08 yields slightly more favorable results with a projected 155 [95% PI: 132 to 178] additional survivors – 19 more than when the ERR is 0.11.

Thus, in this analysis isolating the effect of *Alternative Initiation*, this tobacco use transition has a modest benefit of 136 additional survivors at age 72. Compared to the benefit estimated for

Switching, *Alternative Initiation* has a far more modest effect on survival within a single birth cohort.

6.4.6.1.4.6 Delayed Smoking

Specifications

This Component analysis considers that some individuals who engaged in *Alternative Initiation* – young non-tobacco users who were expected to smoke but instead initiated with Camel Snus – may nevertheless go on to smoke. This *Delayed Smoking* group may reap some benefit from its use of Camel Snus, because their onset of smoking is delayed, but the projected benefit would be less than that for those who continue to use Camel Snus and never go on to smoke.

Because the probability of this secondary tobacco use transition cannot be estimated empirically from the likelihood of use data, analyses assume that 50% of the *Alternative Initiation* group progress to smoking (this parallels the assumption used to assess *Gateway Effect*).

Analysis estimates

Table 6.4.6-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a benefit of 77 [95% PI: 61 to 94] additional survivors. Estimates are modestly higher when the ERR is 0.08 (estimated survival benefit of 87; 95% PI: 70 to 105).

These analyses show that, as expected, *Delayed Smoking* reduces the expected benefit from *Alternative Initiation*. For example, using an ERR of 0.11, *Alternative Initiation* is estimated to increase survival by 136 persons, but this is decreased to 77 if 50% eventually become smokers. Therefore, *Delayed Smoking* decreases the survival benefit of *Alternative Initiation*, while the posited transitions, in aggregate, would still provide a survival benefit.

6.4.6.1.4.7 Additional Initiation

Specifications

This Component analysis isolates the effect of *Additional Initiation* (uptake of Camel Snus among non-tobacco users aged 13-27 who were otherwise not expected to take up smoking). This tobacco use transition confers harm because these individuals would otherwise have avoided all tobacco-related harm. *Additional Initiation* is estimated from the likelihood of use study in which non-tobacco using respondents who were assessed as not being susceptible to smoking estimated their likelihood to take up Camel Snus. Based on extensive documented evidence of tobacco initiation by age in the U.S. population, initiation was limited to ages 13-27, and *Additional Initiation* was estimated at 0.3% within each of the three 5-year age intervals covering this age range.

Analysis estimates

Table 6.4.6-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a decrease of 205 [95% PI: -193 to -217] fewer survivors. Using an ERR of 0.08 yields slightly more favorable results with 145 [95% PI: -134 to -155] fewer survivors, which is 60 more survivors than when the ERR is 0.11.

This analysis suggests that *Additional Initiation*, as expected, has harmful effects on survival in the cohort population. Compared to the positive benefit of *Switching*, the effect is much smaller because *Additional Initiation* is a low-probability event, estimated at 0.3% in the first three 5-year age intervals, and also because the harmful effects of Camel Snus are much lower than those of smoking.

6.4.6.1.4.8 Gateway Effect

Specifications

This Component analysis considers that some of the individuals in the *Additional Initiation* cohort – young non-tobacco users who were not expected to smoke but did initiate with Camel Snus – might eventually begin smoking (*Gateway Effect*). Individuals who experience the *Gateway Effect* tobacco use transition would be substantially harmed because they incur the harms of smoking, which they otherwise would have avoided.

Because the probability of this secondary tobacco use transition cannot be estimated empirically from the likelihood of use data, analyses conservatively assume that 50% of the *Additional Initiation* group progress to smoking.

Analysis estimates

Table 6.4.6-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a decrease of 415 [95% PI: -397 to -435] fewer survivors. Estimates are more favorable when the ERR is 0.08 with 382 [95% PI: -364 to -400] fewer survivors.

These analyses show that, as expected, the *Gateway Effect* transition exacerbates the harm of *Additional Initiation* (Table 6.4.6-2). For example, assuming an ERR of 0.11, when the *Gateway Effect* is experienced by 50% of the *Additional Initiation* group, survival decreases by 210 individuals compared to *Additional Initiation* without any *Gateway Effect*. Compared to the positive benefit of *Switching*, the impact of the *Gateway Effect* is much smaller, suggesting that it can be counteracted by *Switching*; this is explored in tipping point analyses below.

6.4.6.1.4.9 Summary of Component analyses using empirically-derived inputs

The DPM(+1) modeler provides insight into the likely population impact of a Camel Snus MRTP and its proposed modified risk advertising. Relying primarily on empirically-derived estimates of tobacco use transitions as model inputs – both benefits and harms – this comprehensive model

projects that making Camel Snus available as an MRTP would increase survival by approximately 6,000 individuals in a single birth cohort of 1 million males.

Component analyses examining the effect of individual tobacco use transitions in isolation show that the dominant influence on the overall population health effects of a Camel Snus MRTP is from *Switching*. The effects of other transitions are comparatively much smaller, by an order of magnitude. The most impactful adverse transition is *Relapse* following *Diversion from Quitting*, that is, the effect if one presumes that half of the smokers who adopt Camel Snus instead of quitting are thereby caused to resume smoking. This hypothetical effect is estimated to reduce survival by 1,964 (assuming ERR=0.11); the favorable effect of *Switching* (after discounting for *Resumed Smoking)* is approximately 5 times larger. The pattern of results obtained with modeling suggests that even low levels of *Switching* to Camel Snus instead of continuing to smoke are sufficient to overcome the adverse impact of harmful tobacco use transitions that might occur with an MRTP. This proposition is examined in the following section.

6.4.6.2 Tipping point analyses

Unlike the analyses using empirically-derived estimates of tobacco use transitions, which aim to estimate what are deemed to be realistic scenarios, tipping point analyses explore the boundaries of the model to determine where the model outputs project a tipping point between negative and positive population health effects. The analyses discussed above make clear that the biggest source of beneficial effects on population health (survival) is from *Switching* from smoking to Camel Snus (among smokers not likely to quit), which is the behavioral outcome intended by the proposed modified risk advertising for Camel Snus. Accordingly, tipping point analyses seek to determine how much *Switching* is necessary to offset the harmful effects of other tobacco use transitions. As the focus of tipping point analyses are specifically on the beneficial effect of *Switching*, the other beneficial transition in the model – *Alternative Initiation* – is not included in any tipping point analyses (and the effect of subsequent *Delayed Smoking*, which was to reduce those benefits, was, therefore, moot).

In this section, the tipping point is defined as the level of *Switching* that neutralizes the negative effects of the harmful tobacco use transitions in the model; that is, the level of *Switching* at which the net population effect is neutral, that is, near zero. (Other tipping point definitions are considered in the underlying modeling report Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report.) The Master model considers all of the harmful tobacco use transitions defined in Table 6.4.6-1 except *Relapse*, considering the level of *Switching* that would be necessary to overcome the effect of all of the posited harmful transitions. To further test the limits of the effects of *Switching*, several Component analyses use extreme estimates of particular harms. That is, they ask what percent of *Switching* would be necessary to offset even extreme and unrealistic estimates of certain potential harms.

6.4.6.2.1 Master model

6.4.6.2.1.1 Model specifications

The Master model incorporates empirically-derived estimates from the likelihood of use study for all of the harmful primary tobacco use transitions and conservative estimates for the secondary tobacco use transitions *Gateway Effect* and *Resumed Smoking*[15] to assess how much *Switching* is needed to offset these potential harms. The model uses the inputs shown in Table 6.4.6-1, with the exception that *Alternative Initiation*, a beneficial transition, is not included, in order to focus on the beneficial effects of *Switching*. *Gateway Effect* and *Resumed Smoking* are estimated at 50%. Based on the projected use rates from the likelihood of use study, *Diversion from Quitting* varies by age, generally declining from 22.1% to 1.8%. *Additional Initiation* is estimated at 0.3% for the 13-27 age intervals.

As discussed above, the model does not incorporate estimates of *Relapse*, as it cannot be accommodated in the integrated model. To assess the effects of *Relapse*, additional analyses were run in which the tipping point is considered to have been reached when the net positive effect on survival is sufficient to offset the negative effects of *Relapse*. In other words, the tipping point analyses require the effect of *Switching* to be sufficiently favorable to offset the effects of *Relapse*, which were estimated separately. Thus, these tipping point analyses assess how much *Switching* must occur to offset all potential harmful tobacco use transitions.

6.4.6.2.1.2 Model estimates

Incrementally increased rates of *Switching* were tested in these analyses (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report). It is informative to examine the estimates with 0% *Switching*, as this represents the cumulative effect of the posited harmful tobacco use transitions (*i.e.*, the deficit that *Switching* needs to overcome).

When no *Switching* and an ERR of 0.11 is assessed, the potential harm of Camel Snus and its proposed advertising as an MRTP is a reduction in survival estimated to be 943 fewer survivors. The tipping point for *Switching* is 0.61%. That means when 0.61% of smokers who would not otherwise quit smoking switch permanently to Camel Snus in each age interval of follow-up, the harmful effect of other tobacco use transitions is neutralized; that is, the difference in survivors between the counterfactual scenario and base case is 'near zero'. (Note that this does not provide for *Resumed Smoking*; *i.e.*, this is the percentage needed to switch persistently.) For an ERR of 0.08, the harmful tobacco use transitions result in the survival of 771 fewer individuals

[15] As noted above, the harmful secondary tobacco use transition of *Delayed Smoking,* whose effect is to reduce the benefit of *Alternative Initiation*, is not included. As the benefits of *Alternative Initiation,* which is the logical predicate to *Delayed Smoking*, are not included in tipping point analyses, the effect of *Delayed Smoking* cannot be included either.

to age 72. This deficit is overcome by persistent *Switching* at 0.48% in each age interval of follow-up.

Thus, these analyses indicate that if one takes realistic estimates of *Additional Initiation* and *Diversion from Quitting*, and conservative estimates of *Gateway Effect* and *Resumed Smoking*, and uses the conservative estimate of ERR at 0.11, having 0.61% *Switching* persistently to Camel Snus instead of continuing to smoke in each age interval is sufficient to offset any potential harmful tobacco use transitions that might occur.

As noted earlier, the integrated Master model does not incorporate the potential harmful effect of *Relapse*. However, the effect of *Relapse* was assessed separately, and the tipping points were re-estimated so as to offset *Relapse* effects. Assessing *Relapse* conservatively (*i.e.*, assuming 50% of the *Diversion from Quitting* group are caused to *Relapse* to smoking) increases the tipping point for *Switching* to 1.37% and 1.50%, for ERR = 0.08 and 0.11, respectively. In other words, roughly 1.5% of smokers *Switching* persistently to Camel Snus in each age interval of follow-up is sufficient to offset all the potential harmful tobacco use transitions possible with a Camel Snus MRTP.

6.4.6.2.1.3 Sensitivity testing for the value of the ERR

The DPM(+1) model incorporated two estimates of the ERR for Camel Snus compared to smoking – 0.08 and 0.11 – derived from expert consensus about these relative risks (Levy *et al*. 2004). These ERR values were modeled as having some uncertainty, which is incorporated in the PIs. To further explore how the value of the ERR affects the estimated population impact of a Camel Snus MRTP, additional sensitivity analyses were conducted using a variant of the tipping point approach. That is, the question of how high the ERR would need to be (*i.e.*, how small the risk-reduction between smoking and Camel Snus would have to be) to offset the expected population benefit of a Camel Snus MRTP was assessed.

The assessment of variations in the ERR used the same tobacco use transitions shown in Table 6.4.6-1. Under these input assumptions, a range of ERR values was assessed to identify the value of ERR at which the net population effect was near zero – *i.e.*, no benefit or harm. That value is when ERR=0.46, which means as long as the health effect of using Camel Snus is less than 46% of the risk of smoking, a Camel Snus MRTP is expected to have a positive effect on population health. This value of 0.46 is roughly 4 to 6 times higher than the expert consensus value for the ERR (0.08 or 0.11; Levy *et al*. 2004), indicating that there is very substantial headroom for a higher-than-estimated ERR that would still result in a Camel Snus MRTP producing a net benefit to population health. This lends confidence that a Camel Snus MRTP with modified risk advertising is likely to benefit population health.

6.4.6.2.2 Analyses examining extreme rates of harmful tobacco use transitions

To further explore the boundaries of the population effects from the introduction of Camel Snus with modified risk advertising, several analyses were run to examine the projected effects

if particular harmful tobacco use transitions are input at extreme values to determine the amount of *Switching* needed to counteract these posited extreme harms.

6.4.6.2.2.1 Impact of 50% rate for Diversion from Quitting

Specifications

This analysis explores the projected impact when 50% of smokers who were likely to quit are diverted from quitting. (This is in contrast to the empirical estimates for *Diversion from Quitting* from the likelihood of use studies, which range from 1.8% to 22.1% across ages, averaging about 9.5%.)

Analysis estimates

The analysis indicates that, with no *Switching* and an ERR of 0.11, the potential harm of a 50% proportion of *Diversion from Quitting* without any beneficial tobacco use transitions reduces survival by 2,002 in the cohort. The tipping point for *Switching* is 1.29% that is, if 1.29% of smokers in the base case who would not have quit smoking switch to Camel Snus, that harmful effect would be neutralized. For an ERR of 0.08, the posited 50% proportion of *Diversion from Quitting* without any beneficial tobacco use transitions results in survival of 1,477 fewer individuals in the cohort, but 0.90% of smokers *Switching* is sufficient to offset that harm.

Thus, these analyses indicate that if one assumes an extreme situation where half of all smokers in the base case who were going to quit smoking instead switch to Camel Snus, and using the conservative estimate of ERR at 0.11, having 1.29% *Switching* in each age interval of follow-up among smokers not intending to quit is sufficient to neutralize any potential harm.

6.4.6.2.2.2 Impact of Additional Initiation equal to the smoking initiation rate

Specifications

This analysis explores the projected impact if the likelihood of *Additional Initiation* due to a Camel Snus MRTP were to be as high as the likelihood of smoking initiation in the counterfactual case; that is, if Camel Snus attracts as many initiates as smoking attracts, but among youth otherwise not likely to smoke. Specifically, the analysis posits that 13.75% of 13-17-year-olds, 10% of 18-22-year-olds, and 1% of 23-27-year-olds who were not using any tobacco product, and who were not otherwise headed to smoking, would initiate with Camel Snus. (By comparison to these posited rates, which average 8.25% across these age intervals, the empirically-derived estimate for Camel Snus initiation is 0.3% in each of the age groups.)

Analysis estimates

In the extreme situation where *Additional Initiation* is as common as smoking initiation and there are no beneficial tobacco use transitions, the model projects a reduction in survival of 5,557 individuals, assuming an ERR of 0.11. Tipping point analysis indicates that if *Switching* were 4.12%, or just over 4% of continuing smokers switched persistently to Camel Snus instead

of continuing to smoke, the harm from high rates of *Additional Initiation* would be offset. For an ERR of 0.08, the projected reduction in survival is 3,800, which would be completely offset by 2.60% of smokers *Switching* persistently to Camel Snus.

The tipping point analysis reveals that a persistent *Switching* rate of 2.60% (ERR=0.08) to 4.12% (ERR=0.11), across age intervals, would reverse the adverse effect of even these very extreme probabilities of *Additional Initiation*.

6.4.6.2.2.3 Impact of Additional Initiation at 10 times the empirical estimate with 50% Gateway Effect

Specifications

This analysis explores the projected impact if the rate of *Additional Initiation* is 10 times as great as what was estimated from the likelihood of use study Execution 2 (*i.e.*, 3% instead of the estimated 0.3%), 50% of those in the *Additional Initiation* group subsequently progress to smoking (*Gateway Effect*), and there are no countervailing beneficial tobacco use transitions.

Analysis estimates

In the extreme situation (*Additional Initiation* 10 times as great as predicted, 50% *Gateway Effect*, no opposing beneficial transitions and an ERR of 0.11), the model projects a reduction in survival of 4,049 individuals at age 72. The tipping point analysis indicates that 2.80% *Switching* persistently in each age interval of follow-up would be enough to counteract and neutralize this potential harm. For ERR=0.08, the projected reduction in survival is 3,720, which would be overcome by 2.43% of smokers *Switching* to Camel Snus in each age interval of follow-up.

The tipping point analysis reveals that if 2.43% (ERR=0.08) to 2.80% (ERR=0.11) of smokers who would not otherwise quit engaged in persistent *Switching* to Camel Snus in each age interval of follow-up, this would reverse the adverse effect of these extreme rates of *Additional Initiation* and *Gateway Effect*.

6.4.6.2.2.4 Summary of Tipping Point Analyses

The tipping point analyses assess the rates of *Switching* (switching persistently to Camel Snus instead of continued smoking, among smokers who were not headed towards quitting) that would be necessary to overcome potential harms – either all harmful tobacco use transitions or extreme counterfactuals (Component analyses). The DPM(+1) estimates that persistent *Switching* rates of about 1.5% in each age interval of follow-up are sufficient to ensure that the net population effect on mortality is not adverse in the face of all potential harms as estimated in the Master model (*i.e.*, empirically-derived estimates of harmful primary tobacco use transitions and conservative specifications for secondary tobacco use transitions, including *Relapse*). In analyses of hypothetical scenarios using very extreme values for harmful tobacco use transitions, a persistent *Switching* rate of about 4% in each age interval of follow-up is enough to counteract even these extreme hypothetical scenarios.

6.4.6.3 Scaling and extrapolation of the modeling to population-based cohorts

The analyses presented thus far are based on a hypothetical cohort consisting of 1 million males that is followed forward from age 13 to estimate survival at age 72. This section presents two extensions of the analyses. The first scales the results of the analyses to apply to a single cohort that is more realistic in size and gender balance. That is, the *results* are scaled from 1 million males to 4.1 million individuals (the actual size of a single U.S. birth cohort) of mixed gender. The second extrapolation expands the analyses from addressing a single birth cohort to addressing what the effect might be in each of the multiple cohorts that make up the full U.S. population aged 13-72. Each extension is discussed below.

6.4.6.3.1 Scaling the effects modeled for a cohort of 1 million males to a full cohort of mixed gender

The analyses presented thus far are based on a cohort of 1 million males, followed starting at age 13. In reality, there are 4.1 million 13-year-olds in the U.S. of whom 51% are female (U.S. Census Bureau 2016). Analyses suggested that, because the life table for females is different from the male life table, the benefit of the Camel Snus MRTP would be 19% lower for women (*i.e.*, 81% that accruing to males) (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 2, Final Report, Appendix H). Accordingly, one can scale the effects on the entire mixed-gender cohort of 4.1 million[16] by multiplying the estimates from the 1 million male cohort by 3.70271 (4.1 {cohort scaling} * [0.49 {proportion male} +(0.51 {proportion female} * 0.81 {gender correction for mortality differential}]). This is expected to more realistically model population effects, as the true population is, of course, of mixed gender, and the empirically-derived estimates of tobacco use transitions were derived from a mixed-gender sample in the likelihood of use study. The resulting estimated effects on survival for this mixed-gender cohort are shown in Table 6.4.6-3.

As the scaling to a mixed-gender cohort is based on a multiplier applied to the figures in Table 6.4.6-2, the dynamics are identical, but the numbers are on a more realistic scale. Extension of the analyses to scale the Master model (with *Relapse*) results to this mixed-gender cohort indicates that a Camel Snus MRTP would increase survival by 21,000-23,000 lives. On its own, even allowing for 50% *Resumed Smoking*, *Switching* among smokers who would otherwise continue to smoke remains the biggest influence on survival, improving survival by approximately 28,000-30,000. Estimates of tipping points remain the same, as they are unaffected by this scaling.

[16] This mixed-gender cohort analysis, like the male-only cohort analyses, uses the transition probabilities derived from the likelihood of use study, which were based on a sample of mixed gender. Thus, neither the male-only nor mixed-gender analyses adjust for possible gender-based differences in tobacco use transition probabilities.

This extension of the analyses indicates that a Camel Snus MRTP is expected to have substantial beneficial effects on the population, increasing survival at age 72, by 21,000-23,000 in a single mixed-gender birth cohort of 4.1 million.

Table 6.4.6-3: Estimated changes in survival to age 72 in a single birth cohort of 4.1 million males and females, followed from age 13 to age 72

	ERR = 0.11			ERR = 0.08		
Model	**Estimated change in survival**	**95% Posterior Interval**		**Estimated change in survival**	**95% Posterior Interval**	
		Min	**Max**		**Min**	**Max**
Master model	25,249	21,916	28,670	27,304	23,757	30,903
Master model, with *Relapse* ♦	21,013			22,864		
Component analyses††						
Switching	51,560	45,399	57,803	54,204	47,735	60,710
Switching with *Resumed Smoking**	28,518	25,101	31,954	29,966	26,389	33,558
Diversion from Quitting	-1,959	-1,714	-2,211	-1,444	-1,263	-1,629
Diversion from Quitting with *Relapse** ♦	-7,272			-7,006		
Alternative Initiation	504	430	585	574	489	659
Alternative Initiation with *Delayed Smoking**	285	226	348	322	259	389
Additional Initiation	-759	-715	-803	-537	-496	-574
Additional Initiation with *Gateway Effect**	-1,537	-1,470	-1,611	-1,414	-1,348	-1,481

†† Refer to the tobacco use transitions in Table 6.4.6-1 where each tobacco use transition is described.

* Analyses that include secondary tobacco use transitions necessarily must also include their predicate primary transitions. The impact of the secondary transition can be estimated by the difference in survival between the model run with the secondary transition and the model run with only the predicate primary transition.

♦ The estimated change in survival in these model runs incorporates *Relapse* effects. As discussed in this section, *Relapse* in the same age interval cannot be fully incorporated into the DPM(+1), but its effects can be estimated by comparing two counterfactual scenarios. The reduction in projected survival due to *Relapse* is used to reduce the projected survival estimates in model runs that include *Relapse* compared to the same model run without *Relapse*. However, because the difference between the counterfactual scenario and the base case is not estimated directly for counterfactual scenarios incorporating *Relapse*, 95% PIs are not provided.

6.4.6.3.2 Extrapolating the effects modeled for a cohort of 1 million males to multiple cohorts in the current population

The Master model and Component analyses discussed above consider the effect of a Camel Snus MRTP only for single tobacco-naïve cohorts entering their teen years when a Camel Snus MRTP first becomes available. However, this focus on a single cohort does not consider the potential effect of the introduction of a Camel Snus MRTP on other cohorts, particularly those that are already past age 13, and that may also use a Camel Snus MRTP when it becomes available. Notably, it does not assess the potential benefit to people who are already smoking at the time the MRTP with modified risk advertising is introduced and could benefit from *Switching* completely to Camel Snus.

The DPM(+1) is designed to estimate the effect of an intervention on a single cohort that is followed over time to a certain end-point (in this case, from the age of tobacco initiation to age 72). Results from the DPM(+1) single cohort-based model runs were extrapolated to estimate effects in multiple cohorts representing the full population. The current population can be thought of as a series of birth cohorts, each of which has reached a different age at the time the Camel Snus MRTP becomes available. For these multiple cohort analyses, the introduction of the Camel Snus MRTP occurs at different ages for each birth cohort and affects current smokers in addition to never tobacco users. Thus, in aggregate, it aims to estimate the effect of introducing the MRTP to a population of mixed age (13-72 years) and smoking status. Consistent with the single-cohort analyses, the cohorts were grouped into 5-year age intervals, as shown in Table 6.4.6-4.

To assess the effect of introducing a Camel Snus MRTP into each cohort, the model posits that each age group reaches its index age with cigarettes available, but not a Camel Snus MRTP. Each age group then gains access to a Camel Snus MRTP at their "current" age – enabling transitions to Camel Snus as they enter the next 5-year age interval. (So, for example, individuals in the cohort now age 33-37 may initiate or quit smoking up to that age, and then may engage in *Switching* to Camel Snus starting at age 38.) The analyses are based on the estimated tobacco use transitions that make up the Master model (*i.e.*, representing empirically-estimated primary tobacco use transition probabilities and conservative estimates of secondary transitions (except for *Relapse*, which cannot be included in the Master model, as discussed previously). Separate analyses were run assuming an ERR=0.08 and 0.11.

This multiple cohort full population analysis applies the inputs used in the single-cohort analyses (*i.e.*, the 2000 mortality rates, the 2009 smoking initiation rates, the 2005-2008 smoking cessation rates) to multiple cohorts that may have different tobacco use and survival experiences. As such, this extrapolation should be taken only as a heuristic indication of the potential impact on these cohorts.

As in the single-cohort analyses, the modeling was based on a hypothetical cohort of 1 million males in each age interval. Table 6.4.6-4 shows the predicted effect on survival to age 72 for each of these 1 million-person male cohorts. The table shows that a Camel Snus MRTP would

benefit survival for individuals in each of the 5-year age intervals at the time the Camel Snus MRTP is introduced. The estimated magnitude of the benefit is greatest in the younger cohorts, which is expected since smokers in those age intervals have the shortest history of smoking, have the most time available to switch to Camel Snus, and gain the benefit from switching over a longer period of time. Indeed, in some of the older age intervals, many smokers will already have died before the Camel Snus MRTP is introduced. Thus, it is expected that younger individuals will reap the most benefit from the introduction of a Camel Snus MRTP. Conversely, though, the benefits accruing to older individuals are realized sooner, as they are closer to age 72 (the age at which survival is tallied in the model).

Table 6.4.6-4: Estimated change in survival[¶] to age 72 for multiple cohorts of 1 million males each, representing the profile of the current population, by age at the time of an MRTP introduction

Age at MRTP availability		ERR = 0.11			ERR = 0.08		
		Estimated change in survival	95% Posterior Interval		Estimated change in survival	95% Posterior Interval	
For initiation	For switching		Min	Max		Min	Max
13-17	18-22♦	6,819	5,919	7,743	7,374	6,416	8,346
18-22	18-22	6,972	6,078	7,888	7,511	6,562	8,473
23-27†	23-27	5,813	5,075	6,568	6,248	5,466	7,048
	28-32	4,195	3,660	4,747	4,481	3,914	5,066
	33-37	2,196	1,913	2,490	2,345	2,046	2,655
	38-42	1,301	1,134	1,478	1,385	1,208	1,571
	43-47	737	641	838	779	678	885
	48-52	350	304	399	370	322	422
	53-57	123	106	140	130	112	148
	58-62	43	37	50	45	39	52
	63-67*	12	10	13	12	10	14

[¶]Based on the tobacco use transitions in the Master model (Table 6.4.6-1), without adjustment for *Relapse*. The estimates are for a cohort of 1 million males in each age interval.

♦ This cohort cannot engage in *Switching* until it has initiated smoking, which can occur in the 13-17 age interval at the earliest. Hence, the first age for *Switching* is later than the age for initiation.

† Initiation is modeled as ceasing after age 27.

* This is the last age interval during which *Switching* can make a difference in the outcome (survival).

The multiple cohorts of 1 million males each do not represent the size and gender composition of U.S. birth cohorts. To estimate results for a more representative population, the results from Table 6.4.6-4 are adjusted to include females and reflect differential mortality between males and females. For each age interval, differences in survivors shown in Table 6.4.6-4 are adjusted for differences in mortality (19% lower in females than in males) for the age at which the MRTP becomes available within each age interval. Table 6.4.6-5 shows the results for ERR=0.11 and ERR=0.08.

Table 6.4.6-5: Estimated changes in survival[¶] to age 72 for mixed-gender cohorts, sized to the U.S. population aged 13 to 67 at the time of the hypothetical Camel Snus MRTP introduction

Age at MRTP availability		ERR	
For initiation	**For switching**	**0.11**	**0.08**
13-17	18-22♦	126,963	137,034
18-22	18-22	113,964	122,647
23-27†	23-27	90,857	97,402
	28-32	56,773	60,638
	33-37	28,994	30,925
	38-42	15,584	16,548
	43-47	7,979	8,433
	48-52	3,836	4,055
	53-57	1,523	1,606
	58-62	530	549
	63-67*	106	106

[¶]Based on the tobacco use transitions in the Master model (Table 6.4.6-1) without *Relapse*.

♦ This cohort cannot engage in *Switching* until it has initiated smoking, which can occur in the 13-17 age interval at the earliest. Hence, the first age for *Switching* is later than the age for initiation.

† Initiation is modeled as ceasing after age 27.

* This is the last age interval during which *Switching* can make a difference in the outcome (survival).

These analyses suggest that a Camel Snus MRTP would increase survival for individuals in each age interval. Note that these estimates do not include the adverse effects of *Relapse*, which reduces the survival benefit by approximately 12% (Table 6.4.6-2 and Table 6.4.6-3).

While the figures from this full population extrapolation are not precise, together with the primary single-cohort model analyses, the multiple-cohort analysis further emphasizes the potential for a Camel Snus MRTP to provide substantial benefit to population health.

6.4.7 Limitations and Strengths

In advance of actual in-market experience with an MRTP, modeling provides a means of estimating the likely impact of product availability and use on population health. Like all modelers, the DPM(+1) modeler relies on simplifying assumptions about the dynamics of tobacco use and tobacco-related mortality. Importantly, wherever possible, model inputs were based on empirical data, and the model was validated against observed data on mortality in the U.S. (for smoking) and Sweden[17] (for snus use).

[17] This was done in a separate validation exercise (Bachand and Sulsky 2013). The modeling of Camel Snus MRTP effects did not use estimates from the Swedish population; it used U.S.-based smoking mortality statistics, and the specified ERR values to model the effects of snus on mortality, and U.S.-based likelihood of use data to model tobacco use transitions.

The DPM(+1) modeler estimated survival for a hypothetical male cohort of 1 million individuals and used smoking and mortality data for males as inputs. Extrapolating the model to project effects for a single mixed-gender cohort of males and females is based on analyses that estimate the effect on females to be 19% lower than for males. Input probabilities for tobacco use transitions were not differentiated by gender: the empirically-derived probabilities of primary tobacco use transitions are based on data from the entire mixed-gender sample included in the likelihood of use study, and the arbitrary or extreme inputs for secondary tobacco use transitions also are not gender-specific.

Extrapolation of the single-cohort analyses to estimate the effects on the multiple cohorts that make up the current population implicitly assumes that the inputs (smoking and mortality data, tobacco use transition probabilities) will not vary across age cohorts. It is likely that these parameters do vary. Nevertheless, the analysis provides some insight into the scale of the potential benefit of a Camel Snus MRTP on the different cohorts that make up the current U.S. population aged 13-67.

Many inputs to the DPM(+1) modeler are taken from results of the likelihood of use study, which assessed the interest of various subgroups in purchasing Camel Snus for personal trial. Self-reported purchase intent ratings from the likelihood of use study were translated into purchase probabilities (as a proxy for likelihood of use) using an empirically-validated algorithm. It is likely that these projections over-estimate the adoption of Camel Snus. However, the overestimation is likely to apply across the board, and an overall reduction in the use of Camel Snus reduces both benefits and harms, since both depend on use of Camel Snus, just by different subsets of the cohort (*i.e.*, smokers versus non-smokers). Thus, an overall change in the estimated appeal of Camel Snus is unlikely to change the conclusion that the net effects of an MRTP are positive. Indeed, the DPM(+1) model results show that even reducing all of the estimated transition probabilities by 75% (*i.e.*, simulating an across-the-board decrease in use of Camel Snus) does not change the fundamental conclusion that a Camel Snus MRTP would result in a net benefit to population health.

In another respect, using estimates of use based on the likelihood of use study may underestimate use of Camel Snus. The likelihood of use study results are based on a single exposure to a tobacco company advertisement. Repeated exposures may increase interest in a modified risk tobacco product. This mode of communication may also have limited impact because consumers are skeptical of claims made in advertisements and are particularly suspicious of claims made by a tobacco company (Harris Interactive 2013; Byrne *et al*. 2012). Accurate information about reduced risk of Camel Snus compared to smoking from other, more authoritative, sources may increase the appeal of a modified risk tobacco product, particularly to current smokers not interested in quitting.

The modeling results presented here benefit from considerable strengths. The DPM(+1) considers multiple tobacco use transitions that could affect population health. The DPM(+1) modeler itself and the empirical inputs regarding tobacco use and its effects on survival were

validated against population data for smoking (in the U.S.) and snus use (in Sweden)[18]. The DPM(+1) considers the uncertainty around certain parameters and produces PIs that reflect that uncertainty. The model makes conservative assumptions – for example, by not including the benefits of quitting Camel Snus – suggesting that the benefits may be greater than estimated. The results present only the impact on a single cohort of individuals coming into the age of risk for tobacco initiation. Extrapolations of the model results that consider potential effects on the full population, including those who are already smoking, suggest that the beneficial effects of a Camel Snus MRTP would actually be realized by individuals in all age intervals.

6.4.8 Summary

The DPM(+1), a validated modeler for estimating tobacco-related mortality in a population, was used to assess a diverse set of hypothetical scenarios to consider a spectrum of potential benefits and harms from a Camel Snus MRTP order. The DPM(+1) modeler considers primary tobacco use transitions based on estimates empirically-derived from the likelihood of use study, as well as non-empirical estimates of secondary tobacco use transitions that are considered to be conservative. The Master model considers all of the benefits and harms (with separate adjustment for *Relapse*), while Component analyses estimate the effects of particular tobacco use transitions that are sources of benefit or harm. Besides evaluating scenarios considered to be realistic, tipping point analyses evaluate what percentage of current smokers who were not likely to quit – the intended population for a Camel Snus MRTP – would need to switch to Camel Snus (*Switching*) in order to overcome various conservatively-estimated harms to yield a net positive impact on population health (survival).

Model outcomes are expressed as incremental survival of a single U.S. birth cohort comprised of one million individuals who were 13 years of age at the time of MRTP availability. Following a single cohort that enters the age of tobacco initiation at a time when a Camel Snus MRTP with modified risk advertising is (hypothetically) available yields valid estimates of the effects on that cohort. However, it underestimates the total benefit on the U.S. population, because it does not take into account the potential benefit to individuals already 18 or older at the time of a Camel Snus MRTP introduction, many of whom are already smoking, and thus stand to benefit from *Switching* to Camel Snus. Extrapolations estimate the effect of a Camel Snus MRTP order on the full population, for which a Camel Snus MRTP only becomes available at their current age. Although this exercise is less precise, it is important to consider this potential benefit. Accordingly, it is important to consider the total population benefit, counting both a tobacco naïve cohort from age 13 as well as the multiple cohorts that constitute the current U.S. population aged 18 and older, which includes many adult smokers.

[18] This was done in a separate validation exercise (Bachand and Sulsky 2013). The modeling of Camel Snus MRTP effects did not use estimates from the Swedish population; it used U.S.-based smoking mortality statistics, and the specified ERR values to model the effects of snus on mortality, and U.S.-based likelihood of use data to model tobacco use transitions.

6.4.8.1 Net effects on population health (survival) are likely to be positive and unlikely to be negative

The modeling results consistently indicate that Camel Snus is likely to have a net positive benefit on population health, increasing survival for the population as a whole (*i.e.*, decreasing tobacco-related mortality). The Master model, including empirically-derived estimates of primary tobacco use transitions based on the likelihood of use study and employing a conservative ERR of 0.11, indicates that making a Camel Snus MRTP available with modified risk advertising would increase survival to age 72 by nearly 6,000 persons in a single birth cohort of 1 million males that enters its teenage years as the Camel Snus MRTP with modified risk advertising becomes available. Scaling the results to a mixed-gender cohort of 4.1 million individuals indicates that a Camel Snus MRTP would increase survival to age 72 by 21,000 individuals. Considering the full population, which includes adults who are presently smoking, the introduction of the Camel Snus MRTP is estimated to increase survival for individuals in each age interval.

Tipping point analyses using empirically-based estimates of all the potential harmful tobacco use transitions with a Camel Snus MRTP indicate that Camel Snus would offset projected harms if only approximately 1.5% of the intended user population (*i.e.*, current smokers who are not likely to quit) switched completely to Camel Snus in each age interval of follow-up. This suggests that having Camel Snus available with MRTP advertising will likely produce a population health benefit, and, moreover, that net population harm is unlikely.

The modeler uses estimates of the risk reduction due to *Switching* from smoking to Camel Snus that were based on expert estimates. Two estimates were used in these analyses – a 92% reduction in risk (ERR=0.08) and an 89% reduction (ERR=0.11) – and both were modeled with uncertainty. Additionally, a sensitivity analysis using the assumptions included in the Master model, considering all harmful and beneficial tobacco use transitions (after adjustment for *Relapse*), shows that the break-even point where the population is neither benefitted nor harmed, was an ERR of 0.46, or a reduction in risk compared to smoking of 54%. Therefore, even if *Switching* from cigarette smoking to Camel Snus only reduces risk by as little as 50% – much less than the expert estimates of 89%-92% – a Camel Snus MRTP would still have favorable effects on population health.

6.4.8.2 Influence of model inputs on estimated survival

The DPM(+1) outputs demonstrate that the biggest influence on population health and survival is *Switching* – that is, current smokers not likely to quit *Switching* to Camel Snus rather than continuing to smoke. All other tobacco use transitions considered in the modeler are dwarfed by the beneficial effect of this transition in tobacco use. For example, on its own (without other transitions or harms) empirically-derived rates of *Switching* from the likelihood of use study, applied over the life of the cohort, are estimated to yield an increase in survival of about 51,000-54,000 persons in the 13-year-old mixed-gender birth cohort. In contrast, estimating *Gateway Effect* even as high as 50% (among those who initiated Camel Snus and would not otherwise have used tobacco) results in a net loss to survival of about 1,500 in the birth cohort.

Clearly, the *Gateway Effect* has an adverse impact on population health, and steps should be taken to discourage initiation with Camel Snus and further progression to smoking. The modeling results indicate, however, that at the population level, the positive effect of *Switching* is much greater, and the net effect of Camel Snus availability is positive, even in the face of a *Gateway Effect*.

The reasons *Switching* has such a dominant effect on population health is that there are many smokers who are not likely to quit, this large group showed the greatest likelihood of using Camel Snus when presented with modified risk advertising in the likelihood of use study, and continuing smokers have multiple opportunities to engage in *Switching* over their lifetime. Further, the smokers who do switch to Camel Snus stand to gain very significant health benefits, reducing their mortality risk by 89-92% compared to smoking (Levy *et al*. 2004). These factors, in combination, yield very large population health benefits. In contrast, many of the adverse or harmful tobacco use transitions that raise concern about an MRTP apply to much smaller populations and/or to populations that were assessed in the likelihood of use study to have very low likelihood of using Camel Snus. Take *Gateway Effect* as an example. *Gateway Effect* occurs in non-tobacco users who would not otherwise have smoked but take up Camel Snus (the *Additional Initiation* group). The likelihood of use study results indicate that individuals who are not susceptible to smoking also have little interest in trying Camel Snus, suggesting that few of these individuals would adopt Camel Snus. That is why estimating *Gateway Effect* even as high as 50% does not result in large changes in population impact. The same logic applies to beneficial tobacco use transitions such as *Alternative Initiation*, which also occur infrequently, and therefore have minimal impact on net population health.

Parallel analyses were run with two literature-based estimates of risk reduction, an ERR of 0.08 and a more conservative ERR of 0.11. This change made only a modest difference in the estimated population health impact, suggesting that the conclusion that there is a population health benefit does not rest heavily on the precision of the ERR estimate. The modeler also considers the estimates of ERR to be uncertain, and that uncertainty is reflected in the 95% PIs cited in the tables. While the resulting PIs clearly reflect some uncertainty about the magnitude of the benefit of an MRTP for Camel Snus, they do not change the conclusion that there is a benefit. For example, in the Master model using empirically-derived estimates from the likelihood of use study and an ERR of 0.11, the point estimate is 25,249 additional survivors, and the lower bound of the PI is 21,916 survivors per cohort (Table 6.4.6-3) – both reflecting a very substantial population health benefit.

6.4.8.3 Tipping points

Given that *Switching* to Camel Snus is the dominant beneficial tobacco use transition influencing the outcome of the statistical modeling and is the behavior the proposed modified-risk advertisement promotes, tipping point analyses were conducted to assess how much *Switching* is necessary to produce a neutral or beneficial population health impact in the face of extreme estimates of harmful tobacco use transitions. In a Master model using empirically-derived estimates for all primary harmful tobacco use transitions, except *Relapse*, and not

including any other beneficial tobacco use transitions, approximately 1.5% *Switching*, in each age interval of follow-up, is enough to neutralize the potential harmful tobacco use transitions. Estimates based on the likelihood of use study project trial of Camel Snus to be at least this proportion even in the oldest age interval that would benefit from *Switching* and within which the beneficial effect of *Switching* is smallest. As a further context for the 1.5% rate of *Switching* needed to overcome all the posited harms, the projected *Switching* proportions in the two youngest age intervals where *Switching* could occur (18-22, 23-27), and where *Switching* confers the greatest health benefit, are at least 5 times as great as the *Switching* rate required at the tipping point. Thus, tipping point analyses suggest that achievable rates of *Switching* from smoking to Camel Snus can produce a net benefit in population health (survival).

6.4.8.4 Conclusion: Net population health effects of a Camel Snus MRTP with modified risk advertising are likely to be positive and unlikely to be negative

Modeling the effects with empirically-derived estimates of tobacco use transitions indicate a likely increase of 21,000-23,000 survivors to age 72 for a mixed-gender single birth cohort comprised of non-tobacco-users at age 13. The biggest influence on the net population impact is the proportion of smokers *Switching* to Camel Snus instead of continuing to smoke, reducing their health risks. Even in tipping point analyses that make strongly negative assumptions about rates of harmful tobacco use transitions, a rate of *Switching* of less than 4% in each age interval of follow-up would neutralize these extreme rates of harmful tobacco use transitions. Moreover, tipping point analyses using more realistic empirically-based estimates of rates of harmful tobacco use transitions based on the likelihood of use study indicate no population harm even if less than 2% *Switching* occurs in each age interval of follow-up. Sensitivity analyses for the risk reduction between Camel Snus and smoking show that a Camel Snus MRTP with modified risk advertising would likely produce a population health benefit even if the risk reduction is only about 50%, rather than the approximately 90% estimated by experts (Levy *et al*. 2004). Thus, extensive modeling of the likely impact of a Camel Snus MRTP demonstrates that marketing of Camel Snus with modified risk advertising is likely to produce a net benefit to population health and is unlikely to result in net negative effects on population health (survival).

6.4.9 Modeling Results for Execution 3

The proposed modified risk advertisement presented in Execution 3 included claims for significantly reduced risk of lung cancer and respiratory disease for smokers who switched completely from using cigarettes to Camel Snus. This section provides results of the modeling conducted for Execution 3 (complete statistical modeling results for Execution 3 are in Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report). To assess the likely impact of the advertising presented in Execution 3, the DPM(+1) modeler uses the estimates of Camel Snus use from the likelihood of use study Execution 3, as described below.

6.4.9.1 Model using empirically-derived estimates

6.4.9.1.1 Modeler inputs

The DPM(+1) modeler uses empirically-derived estimates as inputs for the probability of all primary tobacco use transitions, based on results of the likelihood of use study Execution 3 (Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Third Execution of Consumer Testing* – Amended Final Report). Individuals with varying tobacco use status were shown the proposed Camel Snus MRTP advertising and rated their interest in trying Camel Snus (likelihood of purchase for trial). These ratings were converted into likelihood of use probabilities (*i.e.*, likelihood of purchase), which formed the basis for the empirical estimates of primary tobacco use transitions. Table 6.4.9-1 below shows the inputs to the model. *Switching* is posited to range from 14.2% to 2.9%, generally decreasing with age (*see* Table 6.4.9-1 below and Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Third Execution of Consumer Testing* – Amended Final Report); *Diversion from Quitting* similarly varies by age, from 16.3% to 1.6%, generally decreasing with age. *Additional Initiation* is estimated at 0.3%, and *Alternative Initiation* at 0.7% for the 13-27 age intervals, based on the empirically-derived projections from the likelihood of use study among respondents ages 18-27 years. Secondary tobacco use transitions (*Gateway Effect, Delayed Smoking, Resumed Smoking,* and *Relapse*) cannot be projected from the likelihood of use study, and are thus included in the analyses as hypothetical (and in many instances, extreme) estimates, with a 50% probability of occurring.

6.4.9.1.2 Summary of results, Execution 3

Using the inputs in Table 6.4.9-1, which incorporate the findings of the likelihood of use study for Execution 3, a series of analyses were run. The results or outputs of the analyses are summarized in Table 6.4.9-2, which shows the estimated effect on survival at age 72 for a hypothetical cohort of one million males[19]. The entries represent the difference in survival between the counterfactual scenario (where some portion of the population uses Camel Snus as an MRTP) and the base case (where only cigarette smoking is an available tobacco use option). Positive numbers indicate improved survival and a benefit to population health in the counterfactual scenario; negative numbers indicate reduced survival and harm to population health. Also shown are the 95% Posterior Intervals (PI), which take into account the uncertainty posited for the input estimates to the base case model, as well as the estimated ERR for Camel Snus. Table 6.4.3-2 shows separate estimates, assuming an ERR of 0.11 and 0.08. Each row represents a set of model inputs, starting with the Master model, which includes almost all the transitions shown in Table 6.4.3-1, followed by Component analyses that isolate particular tobacco use transitions in order to provide insight on the impact of each transition. Primary tobacco use transitions are considered singly. Secondary tobacco use transitions are considered

[19] The DPM(+1) modeler is run on a hypothetical population of 1 million males. Since U.S. birth cohorts are actually about 4.1 million, 51% of whom are female (U.S. Census Bureau 2016), survival estimates are also provided for this more representative mixed-gender birth cohort.

together with their predicate primary transitions. For example, *Gateway Effect* (a secondary transition) can only occur after *Additional Initiation* (a primary transition). Therefore, one analysis considers *Additional Initiation* on its own, and another analysis adds *Gateway Effect*, whose individual contribution can be estimated as the difference between the two analyses. Each analysis is discussed briefly, with reference to Table 6.4.9-1 and Table 6.4.9-2.

Table 6.4.9-1: DPM(+1) inputs for the probability of tobacco use transitions, Execution 3

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact: Benefit or Harm	Modeled Probability	
Primary	Initiation with Camel Snus (instead of abstinence) by never users of tobacco who were *not* likely to initiate smoking	*Additional Initiation*	Harm	0.3%[a]	
Secondary	--- Subsequent progression to smoking due to use of Camel Snus	*Gateway Effect*	Harm	50%[d]	
Primary	Initiation with Camel Snus (instead of smoking) by never users of tobacco who *were* otherwise likely to initiate smoking	*Alternative Initiation*	Benefit	0.7%[a]	
Secondary	--- Subsequent initiation of smoking	*Delayed Smoking*	Harm†	50%[d]	
Primary	Adoption of Camel Snus (instead of smoking) by smokers who were *not* likely to quit	*Switching*	Benefit	**Age Interval**	**% Switching to Camel Snus**
				18-22	9.2
				23-27	14.2
				28-32	12.9
				33-37	9.2
				38-42	7.0
				43-47	7.3
				48-52	5.9
				53-57	3.1
				58-62	3.5
				63-67	2.9
				68+	3.1
Secondary	--- Subsequent return to smoking♦	*Resumed Smoking*	Harm†	50%[b]	

Transition Type	Description of Tobacco Use Transition	Descriptor	Health Impact: Benefit or Harm	Modeled Probability	
				Age Interval	% Using Camel Snus
Primary	Adoption of Camel Snus by smokers who were likely to quit, who either switch to Camel Snus instead of quitting[¶] or who quit, then adopt Camel Snus*	*Diversion from Quitting*	Harm	18-22	8.6
				23-27	16.3
				28-32	13.8
				33-37	10.6
				38-42	12.6
				43-47	5.8
				48-52	4.9
				53-57	2.8
				58-62	5.1
				63-67	2.4
				68+	1.6
Secondary	--- Subsequent relapse to smoking**	*Relapse*	Harm	50%[c]	

--- Indicates a secondary transition among the population undergoing the primary transition immediately above.

† This secondary transition is not net-harmful but rather reduces the benefit of the prior primary transition. For example, if a certain proportion of smokers *Switching* quickly go back to smoking (*Resumed Smoking*), this negates the benefit of *Switching* for that subset, yet they are no worse off than they were before trying Camel Snus.

♦These analyses treat smokers who initially switch to Camel Snus but then return to smoking as though they never use Camel Snus at all, rendering this secondary tobacco use transition neutral in effect (the affected individuals were smoking before the transition and are smoking after the transition). That is, a return to smoking was treated as a reversal of *Switching*, discounting the estimated *Switching* rate. This is conservative, as it does not consider any benefit due to a limited period of use of Camel Snus versus continued smoking.

¶ These analyses do not consider the potential that adoption of Camel Snus might delay rather than completely deter smoking cessation. This is conservative, as it does not count any health benefit that would come from smoking cessation, even if cessation were delayed.

* Smokers who quit and then adopt Camel Snus are modeled as never having quit smoking, with no health benefit attributed to quitting. In essence, these analyses assume these smokers never quit, but adopt Camel Snus instead of quitting.

** The modeler cannot directly accommodate individuals who quit, adopt Camel Snus, and then *Relapse* to smoking within the same age interval. To model *Relapse*, the model was run with the likelihood of quitting reduced, which has roughly the same effect as having a certain proportion of quitters instead

continuing to smoke. This is conservative, as it does not account for any benefit of a period of smoking abstinence or use of Camel Snus. To discern the impact of *Relapse*, survival in in the counterfactual scenario of this run of the model is compared to survival in in the counterfactual scenario of a corresponding run of the model that does not include this effect. The difference in estimates between these two runs of the model is then used to adjust the estimated survival in analyses meant to include the *Relapse* effect.

[a] Applies only to ages 13-27
[b] Not empirically-derived; conservative estimate; reverses percentage of *Switching*
[c] Analyzed separately from other tobacco use transitions with results used to adjust projected survival; transition is not included in the Master model
[d] Applies only to ages 18-32; not empirically-derived; conservative estimate

Table 6.4.9-2: Estimated changes in survival to age 72 in a hypothetical cohort of one million males, followed from age 13 to age 72

	ERR = 0.11			ERR = 0.08		
Model	**Estimated change in survival**	**95% Posterior Interval**		**Estimated change in survival**	**95% Posterior Interval**	
		Min	**Max**		**Min**	**Max**
Master model	6,318	5,481	7,710	6,824	5,938	7,723
Master model, with *Relapse* ♦	5,310			5,768		
Component analyses††						
Switching	12,953	11,409	14,518	13,614	11,997	15,243
Switching with *Resumed Smoking**	7,131	6,278	7,990	7,492	6,602	8,392
Diversion from Quitting	-453	-397	-510	-334	-293	-376
Diversion from Quitting with *Relapse** ♦	-1,698			-1,637		
Alternative Initiation	112	95	130	127	109	147
Alternative Initiation with *Delayed Smoking**	63	50	77	72	58	86
Additional Initiation	-205	-193	-217	-145	-134	-155
Additional Initiation with *Gateway Effect**	-415	-397	-435	-382	-364	-400

†† Refer to the tobacco use transitions in Table 6.4.9-1 where each tobacco use transition is described.

* Analyses that include secondary tobacco use transitions necessarily must also include their predicate primary transitions. The impact of the secondary transition can be estimated by the difference in survival between the model run with the secondary transition and the model run with only the predicate primary transition.

♦ The estimated change in survival in these model runs incorporates *Relapse* effects. As discussed in this section, *Relapse* in the same age interval cannot be fully incorporated into the DPM(+1), but its effects can be estimated by comparing two counterfactual scenarios. The reduction in projected survival due to *Relapse* is used to reduce the projected survival estimates in model runs that include *Relapse* compared to the same model run without *Relapse*. However, because the difference between the counterfactual scenario and the base case is not estimated directly for counterfactual scenarios incorporating *Relapse*, 95% PIs are not provided.

6.4.9.1.3 Master model

6.4.9.1.3.1 Model specifications

The Master model incorporates all tobacco use transitions shown in Table 6.4.9-1, using the estimates of primary beneficial and harmful transitions derived from the likelihood of use study for Execution 3, and hypothetical (and in most instances, extreme) probabilities for secondary harmful transitions. Only *Relapse* (which separate analysis confirmed has relatively small effect) is omitted. Thus, this Master model incorporates all but one (*Relapse*) of the inputs defined in Table 6.4.9-1 and uses empirically-derived estimates from the likelihood of use study Execution 3 for all primary tobacco use transitions.

6.4.9.1.3.2 Model estimates

Table 6.4.9-2 shows the survival predictions from the Master model, which is run on a hypothetical cohort of one million 13-year-old males.

Master Model. This model includes all harmful and beneficial tobacco use transitions, with the exception of *Relapse* in the same age interval, which cannot be integrated into the model. Using the more conservative ERR of 0.11, the model projects a benefit of 6,318 additional survivors [95% PI: 5,481 to 7,710] at age 72 for the counterfactual scenario (Camel Snus MRTP available) versus base case (cigarettes only available). Using an ERR of 0.08 yields slightly more favorable results, with an estimated 6,824 survivors [95% PI: 5,938 to 7,723] – that is, 506, or 8.0%, more survivors to age 72 than the model with the ERR of 0.11.

Master Model with Relapse. Although *Relapse* in the same age interval cannot be integrated into the Master model, the resulting estimate can be adjusted for *Relapse* effects, which are assessed separately. The *Relapse* adjustment reduces the estimated net survival to 5,310 for an ERR=0.11 and to 5,768 for an ERR=0.08.

Therefore, analyses that incorporate all primary harmful tobacco use transitions (based on empirically-derived estimates) and all harmful secondary transitions (based on hypothetical, and, in many instances, extreme, estimates) project the Camel Snus MRTP to result in substantial benefit to population health with more than 5,000 additional survivors in a single birth cohort.

6.4.9.1.3.3 Sensitivity testing for the empirically-based estimates of transitions to Camel Snus

In the Master model, estimates empirically-derived from the likelihood of use study are used as assumptions about the probability of primary tobacco use transitions. These projections are based on self-reported interest in trying Camel Snus given by the study participants that are then applied to an empirical algorithm to estimate the probability of purchase for trial (New Tobacco Product 'Likelihood' Study: An Algorithm to Predict Usage of New Tobacco Products Prior to Market Launch – Methodological Report). Tests of the predictive algorithm indicated

that these projections may over-estimate the actual rate of transitions to use of Camel Snus. However, logically, consistently overestimating use of Camel Snus is not expected to change the conclusion that Camel Snus has a net positive effect on population health (survival), although it would be expected to change the magnitude of the benefit. The reasoning for this rests on the notion that adoption of Camel Snus is responsible for ***both*** the harms and the benefits in the model, with harms or benefits accruing depending on the population in question. So, if adoption of Camel Snus is lower than estimated, across the board, this would likely reduce both the benefits and harms proportionately, leaving unchanged the conclusion that a Camel Snus MRTP yields a population benefit, though reducing the magnitude of the benefit.

Therefore, a variation of the Master model was run in which all of the empirically-derived estimates of primary tobacco use transitions were reduced by 75%, while secondary transitions retained their original probabilities. As expected, that model run also yielded a net population benefit, with the magnitude of the benefit reduced by approximately 73% (1,838 additional survivors based on ERR=0.08, and 1,702 based on ERR=0.11). Thus, the conclusion that a Camel Snus MRTP is likely to benefit population health is robust to even extreme variations in the estimated appeal of Camel Snus, if, in fact, those variations are proportional.

6.4.9.1.4 Examining the contributions of different tobacco use transitions: Component analyses

The Master model assesses the joint effects of multiple tobacco use transitions on projected survival. The Component analyses that follow isolate the influence of specific components on survival. Thus, they do not represent, nor are they intended to represent, realistic scenarios but rather are included to provide conceptual insight into how the Master model inputs, considered in isolation, exert their influence on the model's outputs.

It should be noted that the effect of various components is not independent or additive; that is, one cannot simply sum the effects of all the components and derive the effects seen in the Master model. The different component parameters affect one another. For example, if *Additional Initiation* or *Alternative Initiation* increases, this results in fewer smokers in the next age interval, which in turn moderates the effect of subsequent transitions such as *Switching*.

6.4.9.1.4.1 Switching

Specifications

This Component analysis isolates the effect of *Switching*; that is, the effect of smokers who were not likely to quit smoking who switch completely to Camel Snus. This tobacco use transition confers a health benefit, because these individuals reduce their risk relative to continued smoking. *Switching* is estimated based on the likelihood of use study, which estimated the uptake of Camel Snus among smokers who were not likely to quit. The estimated rates of *Switching* generally decline with age and are assessed in an age-specific way.

Analysis estimates

As shown in Table 6.4.9-2, using the more conservative ERR of 0.11, *Switching* projects a survival benefit of 12,953 [95% PI: 11,409 to 14,518] additional survivors in the birth cohort. Using an ERR of 0.08 yields more favorable results with a projected 13,614 additional survivors [95% PI: 11,997 to 15,243] – approximately 660 more than when the ERR is 0.11 (an increase of 5%).

This analysis estimates the effect of smokers who were not likely to quit smoking who instead switch to Camel Snus, which substantially reduces their health risks. The approximately 13,000-person increase in survival is far greater than the figures estimated in the Master model that included many other tobacco use transitions, both beneficial and harmful. These analyses indicate that the effect of *Switching* is by far the tobacco use transition most affecting the population impact of a Camel Snus MRTP. (Accordingly, it is the focus of tipping point analyses presented subsequently.)

6.4.9.1.4.2 Resumed Smoking

Specifications

This Component analysis considered that some of the smokers not likely to quit who switch to Camel Snus instead of smoking would soon return to smoking. This secondary tobacco use transition would reduce the beneficial population impact of *Switching*. As this secondary tobacco use transition cannot be estimated from the likelihood of use data, it is assigned a probability of occurrence of 50% (*i.e.*, the impact of *Resumed Smoking* is estimated by reducing the empirically-derived estimate of *Switching* by 50%).

Analysis estimates

Table 6.4.9-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, a survival benefit of 7,131 [95% PI: 6,278 to 7,990] additional survivors is projected. Using an ERR of 0.08 yields more favorable results with a projected 7,492 additional survivors [95% PI: 6,602 to 8,392] – approximately 360 more than when the ERR is 0.11 (an increase of 5%).

Assuming that 50% of those *Switching* to Camel Snus quickly return to smoking reduces the projected survival benefit by almost half. (The reduction is slightly less than half because positing that half of those *Switching* return to smoking increases the pool of smokers who can subsequently quit smoking, whereas the model does not incorporate quitting of Camel Snus.) Nevertheless, *Switching*, even with *Resumed Smoking*, is estimated to improve survival to age 72 by at least 7,000 persons in the cohort.

6.4.9.1.4.3 Diversion from Quitting

1.1.3.1.4.3.1 Specifications

This Component analysis isolates the effect of *Diversion from Quitting*, which can be thought of as two potential mechanisms for harm – smokers who otherwise were expected to quit adopt Camel Snus instead of quitting, and smokers who actually do quit and then adopt Camel Snus instead of remaining tobacco free. In both cases, the result is assessed as harmful because Camel Snus carries more risk than abstinence from all tobacco use. Analyses do not distinguish between these two harms because of the assumption that any abstinence in these groups is short-lived and provides no health benefit.

The estimated rates of *Diversion from Quitting* are based on the likelihood of use study, which estimated uptake of Camel Snus among current smokers who were likely to quit. The estimates generally decline with age. Using only estimates from current smokers likely to quit is conservative because estimated rates of Camel Snus adoption among former smokers are much lower in the likelihood of use study (Camel SNUS Modified Risk Messaging: Likelihood of Use among Tobacco Users and Non-Users – *Third Execution of Consumer Testing* – Amended Final Report).

Analysis estimates

Table 6.4.9-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a deficit of 453 [95% PI: -397 to -510] fewer survivors. Using an ERR of 0.08 yields more favorable results with a projected 334 fewer survivors [95% PI: -293 to -376] – 119 more survivors than when the ERR is 0.11.

This analysis estimates the effect of taking up Camel Snus among smokers who were likely to quit smoking, which increases their risk compared to abstaining from all tobacco. The estimated reduction in survival is far smaller than the estimated increase in survival due to *Switching* among smokers who were not likely to quit (Table 6.4.9-2) because the increase in risk going from abstinence to use of Camel Snus is much smaller than the decrease in risk going from smoking to using Camel Snus. Furthermore, based on the results of the likelihood of use study, more smokers fall into the not-likely-to-quit group, and smokers who were likely to quit were less likely to adopt Camel Snus. This suggests that the increased survival due to *Switching* will overcome the harm due to *Diversion from Quitting* to yield a population benefit.

6.4.9.1.4.4 Relapse

Specifications

This Component analysis considers that some of the individuals in the *Diversion from Quitting* group – smokers who were expected to (or did) quit but adopted Camel Snus instead of complete abstinence from all tobacco – might resume smoking (*Relapse*). Individuals who *Relapse* would be substantially harmed because they incur the harms of smoking, which they

otherwise would have avoided but for their use of the MRTP. As described above, the impact of *Relapse*, estimated in a separate analysis, is used to adjust the estimated survival in the *Diversion from Quitting* analysis.

Because the probability of the secondary tobacco use transition of *Relapse* cannot be estimated empirically from the likelihood of use data, analyses include a conservative estimate of 50% of the *Diversion from Quitting* group who would *Relapse* to smoking.

Analysis estimates

Table 6.4.9-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11 and a very conservative estimate of *Relapse* at 50%, the projected survival is a deficit of 1,698 fewer survivors. The estimate (-1,637) is more favorable when the ERR is 0.08. Posterior Intervals cannot be computed for these *Relapse*-adjusted analyses.

These analyses show that, as expected, *Relapse* exacerbates the harm of *Diversion from Quitting*. For example, assuming an ERR of 0.11, *Relapse* decreases survival by 1,245 individuals in the cohort, compared to *Diversion from Quitting* without *Relapse*. This adverse effect is substantial. That it is substantially smaller than the expected beneficial effect of *Switching* suggests that it can be counteracted by sufficient *Switching* among smokers; this will be explored in the tipping point analyses below.

6.4.9.1.4.5 Alternative Initiation

Specifications

This Component analysis isolates the effect of *Alternative Initiation* (uptake of Camel Snus among non-tobacco users aged 13-27 who were otherwise expected to take up smoking). This tobacco use transition confers a benefit because these individuals avoid the excess risk of smoking. *Alternative Initiation* is estimated from the likelihood of use study in which non-tobacco-using respondents who were assessed as susceptible to smoking estimated their likelihood to take up Camel Snus. Based on extensive documented evidence of tobacco initiation by age in the U.S. population, initiation was limited to ages 13-27, and *Alternative Initiation* is estimated at 0.7% within each of the three 5-year age intervals covering this age range.

Analysis estimates

Table 6.4.9-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a benefit of 112 [95% PI: 95 to 130] additional survivors. Using an ERR of 0.08 yields slightly more favorable results with a projected 127 [95% PI: 109 to 147] additional survivors – 15 more than when the ERR is 0.11.

Thus, in this analysis isolating the effect of *Alternative Initiation*, this tobacco use transition has a modest benefit of 112 additional survivors at age 72. Compared to the benefit estimated for

Switching, *Alternative Initiation* has a far more modest effect on survival within a single birth cohort.

6.4.9.1.4.6 Delayed Smoking

Specifications

This Component analysis considers that some individuals who engaged in *Alternative Initiation* – young non-tobacco users who were expected to smoke but instead initiated with Camel Snus – may nevertheless go on to smoke. This *Delayed Smoking* group may reap some benefit from its use of Camel Snus, because their onset of smoking is delayed, but the projected benefit would be less than that for those who continue to use Camel Snus and never go on to smoke.

Because the probability of this secondary tobacco use transition cannot be estimated empirically from the likelihood of use data, analyses assume that 50% of the *Alternative Initiation* group progress to smoking (this parallels the assumption used to assess *Gateway Effect*).

Analysis estimates

Table 6.4.9-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a benefit of 63 [95% PI: 50 to 77] additional survivors. Estimates are modestly higher when the ERR is 0.08 (estimated survival benefit of 72; 95% PI: 58 to 86).

These analyses show that, as expected, *Delayed Smoking* reduces the expected benefit from *Alternative Initiation*. For example, using an ERR of 0.11, *Alternative Initiation* is estimated to increase survival by 112 persons, but this is decreased to 63 if 50% eventually become smokers. Therefore, *Delayed Smoking* decreases the survival benefit of *Alternative Initiation*, while the posited transitions, in aggregate, would still provide a survival benefit.

6.4.9.1.4.7 Additional Initiation

Specifications

This Component analysis isolates the effect of *Additional Initiation* (uptake of Camel Snus among non-tobacco users aged 13-27 who were otherwise not expected to take up smoking). This tobacco use transition confers harm because these individuals would otherwise have avoided all tobacco-related harm. *Additional Initiation* is estimated from the likelihood of use study in which non-tobacco using respondents who were assessed as not being susceptible to smoking estimated their likelihood to take up Camel Snus. Based on extensive documented evidence of tobacco initiation by age in the U.S. population, initiation was limited to ages 13-27, and *Additional Initiation* was estimated at 0.3% within each of the three 5-year age intervals covering this age range.

Analysis estimates

Table 6.4.9-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a decrease of 205 [95% PI: -193 to -217] fewer survivors. Using an ERR of 0.08 yields slightly more favorable results with 145 [95% PI: -134 to -155] fewer survivors, which is 60 more survivors than when the ERR is 0.11.

This analysis suggests that *Additional Initiation*, as expected, has harmful effects on survival in the cohort population. Compared to the positive benefit of *Switching*, the effect is much smaller because *Additional Initiation* is a low-probability event, estimated at 0.3% in the first three 5-year age intervals, and also because the harmful effects of Camel Snus are much lower than those of smoking.

6.4.9.1.4.8 Gateway Effect

Specifications

This Component analysis considers that some of the individuals in the *Additional Initiation* cohort – young non-tobacco users who were not expected to smoke but did initiate with Camel Snus – might eventually begin smoking (*Gateway Effect*). Individuals who experience the *Gateway Effect* tobacco use transition would be substantially harmed because they incur the harms of smoking, which they otherwise would have avoided.

Because the probability of this secondary tobacco use transition cannot be estimated empirically from the likelihood of use data, analyses conservatively assume that 50% of the *Additional Initiation* group progress to smoking.

Analysis estimates

Table 6.4.9-2 shows the predictions from this analysis. Using the more conservative ERR of 0.11, the projected survival is a decrease of 415 [95% PI: -397 to -435] fewer survivors. Estimates are more favorable when the ERR is 0.08 with 382 [95% PI: -364 to -400] fewer survivors.

These analyses show that, as expected, the *Gateway Effect* transition exacerbates the harm of *Additional Initiation* (Table 6.4.9-2). For example, assuming an ERR of 0.11, when the *Gateway Effect* is experienced by 50% of the *Additional Initiation* group, survival decreases by 210 individuals compared to *Additional Initiation* without any *Gateway Effect*. Compared to the positive benefit of *Switching*, the impact of the *Gateway Effect* is much smaller, suggesting that it can be counteracted by *Switching*; this is explored in tipping point analyses below.

6.4.9.1.4.9 Summary of Component analyses using empirically-derived inputs

The DPM(+1) model provides insight into the likely population impact of a Camel Snus MRTP and its proposed modified risk advertising. Relying primarily on empirically-derived estimates of tobacco use transitions as model inputs – both benefits and harms – this comprehensive model

projects that making Camel Snus available as an MRTP would increase survival by approximately 6,000 individuals in a single birth cohort of 1 million males.

Component analyses examining the effect of individual tobacco use transitions in isolation show that the dominant influence on the overall population health effects of a Camel Snus MRTP is from *Switching*. The effects of other transitions are comparatively much smaller, by an order of magnitude. The most impactful adverse transition is *Relapse* following *Diversion from Quitting*, that is, the effect if one presumes that half of the smokers who adopt Camel Snus instead of quitting are thereby caused to resume smoking. This hypothetical effect is estimated to reduce survival by 1,698 (assuming ERR=0.11); the favorable effect of *Switching* (after discounting for *Resumed Smoking)* is approximately 5.5 times larger. The pattern of results obtained with modeling suggests that even low levels of *Switching* to Camel Snus instead of continuing to smoke are sufficient to overcome the adverse impact of harmful tobacco use transitions that might occur with an MRTP. This proposition is examined in the following section.

6.4.9.2 Tipping point analyses

Unlike the analyses using empirically-derived estimates of tobacco use transitions, which aim to estimate what are deemed to be realistic scenarios, tipping point analyses explore the boundaries of the model to determine where the model outputs project a tipping point between negative and positive population health effects. The analyses discussed above make clear that the biggest source of beneficial effects on population health (survival) is from *Switching* from smoking to Camel Snus (among smokers not likely to quit), which is the behavioral outcome intended by the proposed modified risk advertising for Camel Snus. Accordingly, tipping point analyses seek to determine how much *Switching* is necessary to offset the harmful effects of other tobacco use transitions. As the focus of tipping point analyses are specifically on the beneficial effect of *Switching*, the other beneficial transition in the model – *Alternative Initiation* – is not included in any tipping point analyses (and the effect of subsequent *Delayed Smoking*, which was to reduce those benefits, was, therefore, moot).

In this section, the tipping point is defined as the level of *Switching* that neutralizes the negative effects of the harmful tobacco use transitions in the model; that is, the level of *Switching* at which the net population effect is neutral, that is, near zero. (Other tipping point definitions are considered in the underlying modeling report Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report.) The Master model considers all of the harmful tobacco use transitions defined in Table 6.4.9-1 except *Relapse*, considering the level of *Switching* that would be necessary to overcome the effect of all of the posited harmful transitions. To further test the limits of the effects of *Switching*, several Component analyses use extreme estimates of particular harms. That is, they ask what percent of *Switching* would be necessary to offset even extreme and unrealistic estimates of certain potential harms.

6.4.9.2.1 Master model

6.4.9.2.1.1 Model specifications

The Master model incorporates empirically-derived estimates from the likelihood of use study for all of the harmful primary tobacco use transitions and conservative estimates for the secondary tobacco use transitions *Gateway Effect* and *Resumed Smoking*[20] to assess how much *Switching* is needed to offset these potential harms. The model uses the inputs shown in Table 6.4.9-1, with the exception that *Alternative Initiation*, a beneficial transition, is not included, in order to focus on the beneficial effects of *Switching*. *Gateway Effect* and *Resumed Smoking* are estimated at 50%. Based on the projected use rates from the likelihood of use study, *Diversion from Quitting* varies by age, generally declining from 16.3% to 1.6%. *Additional Initiation* is estimated at 0.3% for the 13-27 age intervals.

As discussed above, the model does not incorporate estimates of *Relapse*, as it cannot be accommodated in the integrated model. To assess the effects of *Relapse*, additional analyses were run in which the tipping point is considered to have been reached when the net positive effect on survival is sufficient to offset the negative effects of *Relapse*. In other words, the tipping point analyses require the effect of *Switching* to be sufficiently favorable to offset the effects of *Relapse*, which were estimated separately. Thus, these tipping point analyses assess how much *Switching* must occur to offset all potential harmful tobacco use transitions.

6.4.9.2.1.2 Model estimates

Incrementally increased rates of *Switching* were tested in these analyses (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report). It is informative to examine the estimates with 0% *Switching*, as this represents the cumulative effect of the posited harmful tobacco use transitions (*i.e.*, the deficit that *Switching* needs to overcome).

When no *Switching* and an ERR of 0.11 is assessed, the potential harm of Camel Snus and its proposed advertising as an MRTP is a reduction in survival estimated to be 867 fewer survivors. The tipping point for *Switching* is 0.56%. That means when 0.56% of smokers who would not otherwise quit smoking switch permanently to Camel Snus in each age interval of follow-up, the harmful effect of other tobacco use transitions is neutralized; that is, the difference in survivors between the counterfactual scenario and base case is 'near zero'. (Note that this does not provide for *Resumed Smoking*; *i.e.*, this is the percentage needed to switch persistently.) For an ERR of 0.08, the harmful tobacco use transitions result in the survival of 715 fewer individuals

[20] As noted above, the harmful secondary tobacco use transition of *Delayed Smoking,* whose effect is to reduce the benefit of *Alternative Initiation*, is not included. As the benefits of *Alternative Initiation,* which is the logical predicate to *Delayed Smoking*, are not included in tipping point analyses, the effect of *Delayed Smoking* cannot be included either.

to age 72. This deficit is overcome by persistent *Switching* at 0.44% in each age interval of follow-up.

Thus, these analyses indicate that if one takes realistic estimates of *Additional Initiation* and *Diversion from Quitting*, and conservative estimates of *Gateway Effect* and *Resumed Smoking*, and uses the conservative estimate of ERR at 0.11, having 0.56% *Switching* persistently to Camel Snus instead of continuing to smoke in each age interval is sufficient to offset any potential harmful tobacco use transitions that might occur.

As noted earlier, the integrated Master model does not incorporate the potential harmful effect of *Relapse*. However, the effect of *Relapse* was assessed separately, and the tipping points were re-estimated so as to offset *Relapse* effects. Assessing *Relapse* conservatively (*i.e.*, assuming 50% of the *Diversion from Quitting* group are caused to *Relapse* to smoking) increases the tipping point for *Switching* to 1.21% and 1.33%, for ERR = 0.08 and 0.11, respectively. In other words, slightly more than 1% of smokers *Switching* persistently to Camel Snus in each age interval of follow-up is sufficient to offset all the potential harmful tobacco use transitions possible with a Camel Snus MRTP.

6.4.9.2.1.3 Sensitivity testing for the value of the ERR

The DPM(+1) modeler incorporated two estimates of the ERR for Camel Snus compared to smoking – 0.08 and 0.11 – derived from expert consensus about these relative risks (Levy *et al*. 2004). These ERR values were modeled as having some uncertainty, which is incorporated in the PIs. To further explore how the value of the ERR affects the estimated population impact of a Camel Snus MRTP, additional sensitivity analyses were conducted using a variant of the tipping point approach. That is, the question of how high the ERR would need to be (*i.e.*, how small the risk-reduction between smoking and Camel Snus would have to be) to offset the expected population benefit of a Camel Snus MRTP was assessed.

The assessment of variations in the ERR used the same tobacco use transitions shown in Table 6.4.9-1. Under these input assumptions, a range of ERR values was assessed to identify the value of ERR at which the net population effect was near zero – *i.e.*, no benefit or harm. That value is when ERR=0.47, which means as long as the health effect of using Camel Snus is less than 47% of the risk of smoking, a Camel Snus MRTP is expected to have a positive effect on population health. This value of 0.47 is roughly 4 to 6 times higher than the expert consensus value for the ERR (0.08 or 0.11; Levy *et al*. 2004), indicating that there is very substantial headroom for a higher-than-estimated ERR that would still result in a Camel Snus MRTP producing a net benefit to population health. This lends confidence that a Camel Snus MRTP with modified risk advertising is likely to benefit population health.

6.4.9.2.2 Analyses examining extreme rates of harmful tobacco use transitions

To further explore the boundaries of the population effects from the introduction of Camel Snus with modified risk advertising, several analyses were run to examine the projected effects

if particular harmful tobacco use transitions are input at extreme values to determine the amount of *Switching* needed to counteract these posited extreme harms.

6.4.9.2.2.1 Impact of 50% rate for Diversion from Quitting

Specifications

This analysis explores the projected impact when 50% of smokers who were likely to quit are diverted from quitting. (This is in contrast to the empirical estimates for *Diversion from Quitting* from the likelihood of use studies, which range from 1.6% to 16.3% across ages, averaging about 7.5%.)

Analysis estimates

The analysis indicates that, with no *Switching* and an ERR of 0.11, the potential harm of a 50% proportion of *Diversion from Quitting* without any beneficial tobacco use transitions reduces survival by 2,002 in the cohort. The tipping point for *Switching* is 1.29% that is, if 1.29% of smokers in the base case who would not have quit smoking switch to Camel Snus, that harmful effect would be neutralized. For an ERR of 0.08, the posited 50% proportion of *Diversion from Quitting* without any beneficial tobacco use transitions results in survival of 1,477 fewer individuals in the cohort, but 0.90% of smokers *Switching* is sufficient to offset that harm.

Thus, these analyses indicate that if one assumes an extreme situation where half of all smokers in the base case who were going to quit smoking instead switch to Camel Snus, and using the conservative estimate of ERR at 0.11, having 1.29% *Switching* in each age interval of follow-up among smokers not intending to quit is sufficient to neutralize any potential harm.

6.4.9.2.2.2 Impact of Additional Initiation equal to the smoking initiation rate

Specifications

This analysis explores the projected impact if the likelihood of *Additional Initiation* due to a Camel Snus MRTP were to be as high as the likelihood of smoking initiation in the counterfactual case; that is, if Camel Snus attracts as many initiates as smoking attracts, but among youth otherwise not likely to smoke. Specifically, the analysis posits that 13.75% of 13-17-year-olds, 10% of 18-22-year-olds, and 1% of 23-27-year-olds who were not using any tobacco product, and who were not otherwise headed to smoking, would initiate with Camel Snus. (By comparison to these posited rates, which average 8.25% across these age intervals, the empirically-derived estimate for Camel Snus initiation is 0.3% in each of the age groups.)

Analysis estimates

In the extreme situation where *Additional Initiation* is as common as smoking initiation and there are no beneficial tobacco use transitions, the model projects a reduction in survival of 5,557 individuals, assuming an ERR of 0.11. Tipping point analysis indicates that if *Switching* were 4.12%, or just over 4% of continuing smokers switched persistently to Camel Snus instead

of continuing to smoke, the harm from high rates of *Additional Initiation* would be offset. For an ERR of 0.08, the projected reduction in survival is 3,800, which would be completely offset by 2.60% of smokers *Switching* persistently to Camel Snus.

The tipping point analysis reveals that a persistent *Switching* rate of 2.60% (ERR=0.08) to 4.12% (ERR=0.11), across age intervals, would reverse the adverse effect of even these very extreme probabilities of *Additional Initiation*.

6.4.9.2.2.3 Impact of Additional Initiation at 10 times the empirical estimate with 50% Gateway Effect

Specifications

This analysis explores the projected impact if the rate of *Additional Initiation* is 10 times as great as what was estimated from the likelihood of use study Execution 3 (*i.e.*, 3% instead of the estimated 0.3%), 50% of those in the *Additional Initiation* group subsequently progress to smoking (*Gateway Effect*), and there are no countervailing beneficial tobacco use transitions.

Analysis estimates

In the extreme situation (*Additional Initiation* 10 times as great as predicted, 50% *Gateway Effect*, no opposing beneficial transitions and an ERR of 0.11), the model projects a reduction in survival of 4,049 individuals at age 72. The tipping point analysis indicates that 2.80% *Switching* persistently in each age interval of follow-up would be enough to counteract and neutralize this potential harm. For ERR=0.08, the projected reduction in survival is 3,720, which would be overcome by 2.43% of smokers *Switching* to Camel Snus in each age interval of follow-up.

The tipping point analysis reveals that if 2.43% (ERR=0.08) to 2.80% (ERR=0.11) of smokers who would not otherwise quit engaged in persistent *Switching* to Camel Snus in each age interval of follow-up, this would reverse the adverse effect of these extreme rates of *Additional Initiation* and *Gateway Effect*.

6.4.9.2.2.4 Summary of Tipping Point Analyses

The tipping point analyses assess the rates of *Switching* (switching persistently to Camel Snus instead of continued smoking, among smokers who were not headed towards quitting) that would be necessary to overcome potential harms – either all harmful tobacco use transitions or extreme counterfactuals (Component analyses). The DPM(+1) estimates that persistent *Switching* rates of about 1% in each age interval of follow-up are sufficient to ensure that the net population effect on mortality is not adverse in the face of all potential harms as estimated in the Master model (*i.e.*, empirically-derived estimates of harmful primary tobacco use transitions and conservative specifications for secondary tobacco use transitions, including *Relapse*). In analyses of hypothetical scenarios using very extreme values for harmful tobacco use transitions, a persistent *Switching* rate of 4% or less in each age interval of follow-up is enough to counteract even these extreme hypothetical scenarios.

6.4.9.3 Scaling and extrapolation of the modeling to population-based cohorts

The analyses presented thus far are based on a hypothetical cohort consisting of 1 million males that is followed forward from age 13 to estimate survival at age 72. This section presents two extensions of the analyses. The first scales the results of the analyses to apply to a single cohort that is more realistic in size and gender balance. That is, the *results* are scaled from 1 million males to 4.1 million individuals (the actual size of a single U.S. birth cohort) of mixed gender. The second extrapolation expands the analyses from addressing a single birth cohort to addressing what the effect might be in each of the multiple cohorts that make up the full U.S. population aged 13-72. Each extension is discussed below.

6.4.9.3.1 Scaling the effects modeled for a cohort of 1 million males to a full cohort of mixed gender

The analyses presented thus far are based on a cohort of 1 million males, followed starting at age 13. In reality, there are 4.1 million 13-year-olds in the U.S. of whom 51% are female (U.S. Census Bureau 2016). Analyses suggested that, because the life table for females is different from the male life table, the benefit of the Camel Snus MRTP would be 19% lower for women (*i.e.*, 81% that accruing to males) (Assessing the Population Health Effects of Camel SNUS and Its Proposed Marketing as a Modified-Risk Tobacco Product – Statistical Modeling Using the Dynamic Population Modeler Execution 3, Final Report, Appendix H). Accordingly, one can scale the effects on the entire mixed-gender cohort of 4.1 million[21] by multiplying the estimates from the 1 million male cohort by 3.70271 (4.1 {cohort scaling} * [0.49 {proportion male} +(0.51 {proportion female} * 0.81 {gender correction for mortality differential}]). This is expected to more realistically model population effects, as the true population is, of course, of mixed gender, and the empirically-derived estimates of tobacco use transitions were derived from a mixed-gender sample in the likelihood of use study. The resulting estimated effects on survival for this mixed-gender cohort are shown in Table 6.4.9-3.

As the scaling to a mixed-gender cohort is based on a multiplier applied to the figures in Table 6.4.9-2, the dynamics are identical, but the numbers are on a more realistic scale. Extension of the analyses to scale the Master model (with *Relapse*) results to this mixed-gender cohort indicate that a Camel Snus MRTP would increase survival by approximately 20,000-21,000 lives. On its own, even allowing for 50% *Resumed Smoking*, *Switching* among smokers who would otherwise continue to smoke remains the biggest influence on survival, improving survival by approximately 26,000-27,000. Estimates of tipping points remain the same, as they are unaffected by this scaling.

[21] This mixed-gender cohort analysis, like the male-only cohort analyses, uses the transition probabilities derived from the likelihood of use study, which were based on a sample of mixed gender. Thus, neither the male-only nor mixed-gender analyses adjust for possible gender-based differences in tobacco use transition probabilities.

This extension of the analyses indicates that a Camel Snus MRTP is expected to have substantial beneficial effects on the population, increasing survival at age 72, by 20,000-21,000 in a single mixed-gender birth cohort of 4.1 million.

Table 6.4.9-3: Estimated changes in survival to age 72 in a single birth cohort of 4.1 million males and females, followed from age 13 to age 72

	ERR = 0.11			ERR = 0.08		
Model	**Estimated change in survival**	**95% Posterior Interval**		**Estimated change in survival**	**95% Posterior Interval**	
		Min	**Max**		**Min**	**Max**
Master model	23,394	20,295	28,548	25,267	21,987	28,596
Master model, with *Relapse* ♦	19,661			21,357		
Component analyses††						
Switching	47,961	42,244	53,756	50,409	44,421	56,440
Switching with *Resumed Smoking**	26,404	23,246	29,585	27,741	24,445	31,073
Diversion from Quitting	-1,677	-1,470	-1,888	-1,237	-1,085	-1,392
Diversion from Quitting with *Relapse** ♦	-6,287			-6,061		
Alternative Initiation	415	352	481	470	404	544
Alternative Initiation with *Delayed Smoking**	233	185	285	267	215	318
Additional Initiation	-759	-715	-803	-537	-496	-574
Additional Initiation with *Gateway Effect**	-1,537	-1,470	-1,611	-1,414	-1,348	-1,481

†† Refer to the tobacco use transitions in Table 6.4.9-1 where each tobacco use transition is described.

* Analyses that include secondary tobacco use transitions necessarily must also include their predicate primary transitions. The impact of the secondary transition can be estimated by the difference in survival between the model run with the secondary transition and the model run with only the predicate primary transition.

♦ The estimated change in survival in these model runs incorporates *Relapse* effects. As discussed in this section, *Relapse* in the same age interval cannot be fully incorporated into the DPM(+1), but its effects can be estimated by comparing two counterfactual scenarios. The reduction in projected survival due to *Relapse* is used to reduce the projected survival estimates in model runs that include *Relapse* compared to the same model run without *Relapse*. However, because the difference between the counterfactual scenario and the base case is not estimated directly for counterfactual scenarios incorporating *Relapse*, 95% PIs are not provided.

6.4.9.3.2 Extrapolating the effects modeled for a cohort of 1 million males to multiple cohorts in the current population

The Master model and Component analyses discussed above consider the effect of a Camel Snus MRTP only for single tobacco-naïve cohorts entering their teen years when a Camel Snus MRTP first becomes available. However, this focus on a single cohort does not consider the potential effect of the introduction of a Camel Snus MRTP on other cohorts, particularly those that are already past age 13, and that may also use a Camel Snus MRTP when it becomes available. Notably, it does not assess the potential benefit to people who are already smoking at the time the MRTP with modified risk advertising is introduced and could benefit from *Switching* completely to Camel Snus.

The DPM(+1) is designed to estimate the effect of an intervention on a single cohort that is followed over time to a certain end-point (in this case, from the age of tobacco initiation to age 72). Results from the DPM(+1) single cohort-based model runs were extrapolated to estimate effects in multiple cohorts representing the full population. The current population can be thought of as a series of birth cohorts, each of which has reached a different age at the time the Camel Snus MRTP becomes available. For these multiple cohort analyses, the introduction of the Camel Snus MRTP occurs at different ages for each birth cohort and affects current smokers in addition to never tobacco users. Thus, in aggregate, it aims to estimate the effect of introducing the MRTP to a population of mixed age (13-72 years) and smoking status. Consistent with the single-cohort analyses, the cohorts were grouped into 5-year age intervals, as shown in Table 6.4.9-4.

To assess the effect of introducing a Camel Snus MRTP into each cohort, the model posits that each age group reaches its index age with cigarettes available, but not a Camel Snus MRTP. Each age group then gains access to a Camel Snus MRTP at their "current" age – enabling transitions to Camel Snus as they enter the next 5-year age interval. (So, for example, individuals in the cohort now age 33-37 may initiate or quit smoking up to that age, and then may engage in *Switching* to Camel Snus starting at age 38.) The analyses are based on the estimated tobacco use transitions that make up the Master model (*i.e.*, representing empirically-estimated primary tobacco use transition probabilities and conservative estimates of secondary transitions except for *Relapse*, which cannot be included in the Master model, as discussed previously). Separate analyses were run assuming an ERR=0.08 and 0.11.

This multiple cohort full population analysis applies the inputs used in the single-cohort analyses (*i.e.*, the 2000 mortality rates, the 2009 smoking initiation rates, the 2005-2008 smoking cessation rates) to multiple cohorts that may have different tobacco use and survival experiences. As such, this extrapolation should be taken only as a heuristic indication of the potential impact on these cohorts.

As in the single-cohort analyses, the modeling was based on a hypothetical cohort of 1 million males in each age interval. Table 6.4.9-4 shows the predicted effect on survival to age 72 for each of these 1 million male cohorts. The table shows that a Camel Snus MRTP would benefit

survival for individuals in each of the 5-year age intervals at the time the Camel Snus MRTP is introduced. The estimated magnitude of the benefit is greatest in the younger cohorts, which is expected since smokers in those age intervals have the shortest history of smoking, have the most time available to switch to Camel Snus, and gain the benefit from switching over a longer period of time. Indeed, in some of the older age intervals, many smokers will already have died before the Camel Snus MRTP is introduced. Thus, it is expected that younger individuals will reap the most benefit from the introduction of a Camel Snus MRTP. Conversely, though, the benefits accruing to older individuals are realized sooner, as they are closer to age 72 (the age at which survival is tallied in the model).

Table 6.4.9-4: Estimated change in survival[¶] to age 72 for multiple cohorts of 1 million males each, representing the profile of the current population, by age at the time of an MRTP introduction

Age at MRTP availability		ERR = 0.11			ERR = 0.08		
		Estimated change in survival	95% Posterior Interval		Estimated change in survival	95% Posterior Interval	
For initiation	For switching		Min	Max		Min	Max
13-17	18-22♦	6,318	5,481	7,170	6,824	5,938	7,723
18-22	18-22	6,470	5,642	7,312	6,959	6,080	7,848
23-27†	23-27	5,703	4,983	6,439	6,120	5,356	6,898
	28-32	3,844	3,353	4,352	4,112	3,589	4,651
	33-37	2,249	1,959	2,549	2,399	2,093	2,716
	38-42	1,329	1,157	1,510	1,414	1,233	1,605
	43-47	807	702	917	850	741	966
	48-52	373	324	425	392	341	446
	53-57	133	115	152	140	121	159
	58-62	55	48	63	58	50	67
	63-67*	12	11	14	13	11	15

[¶] Based on the tobacco use transitions in the Master model (Table 6.4.9-1), without adjustment for *Relapse*. The estimates are for a cohort of 1 million males in each age interval.

♦ This cohort cannot engage in *Switching* until it has initiated smoking, which can occur in the 13-17 age interval at the earliest. Hence, the first age for *Switching* is later than the age for initiation.

† Initiation is modeled as ceasing after age 27.

* This is the last age interval during which *Switching* can make a difference in the outcome (survival).

The multiple cohorts of 1 million males each do not represent the size and gender composition of U.S. birth cohorts. To estimate results for a more representative population, the results from Table 6.4.9-4 are adjusted to include females and reflect differential mortality between males and females. For each age interval, differences in survivors shown in Table 6.4.9-4 are adjusted for differences in mortality (19% lower in females than in males) for the age at which the MRTP becomes available within each age interval. Table 6.4.9-5 shows the results for ERR=0.11 and ERR=0.08.

Table 6.4.9-5: Estimated changes in survival[¶] to age 72 for mixed-gender cohorts, sized to the U.S. population aged 13 to 67 at the time of the hypothetical Camel Snus MRTP introduction

Age at MRTP availability		ERR	
For initiation	**For switching**	**0.11**	**0.08**
13-17	18-22♦	117,729	126,889
18-22	18-22	108,509	116,586
23-27†	23-27	86,672	92,890
	28-32	54,126	57,839
	33-37	29,665	31,614
	38-42	16,334	17,312
	43-47	8,661	9,117
	48-52	4,104	4,315
	53-57	1,725	1,817
	58-62	645	684
	63-67*	106	115

[¶]Based on the tobacco use transitions in the Master model (Table 6.4.9-1) without *Relapse*.
♦ This cohort cannot engage in *Switching* until it has initiated smoking, which can occur in the 13-17 age interval at the earliest. Hence, the first age for *Switching* is later than the age for initiation.
† Initiation is modeled as ceasing after age 27.
* This is the last age interval during which *Switching* can make a difference in the outcome (survival).

These analyses suggest that a Camel Snus MRTP would increase survival for individuals in each age interval. Note that these estimates do not include the adverse effects of *Relapse*, which reduces the survival benefit by approximately 16% (Table 6.4.9-2 and Table 6.4.9-3).

While the figures from this full population extrapolation are not precise, together with the primary single-cohort model analyses, the multiple-cohort analysis further emphasizes the potential for a Camel Snus MRTP to provide substantial benefit to population health.

6.4.10 Limitations and Strengths

In advance of actual in-market experience with an MRTP, modeling provides a means of estimating the likely impact of product availability and use on population health. Like all modelers, the DPM(+1) modeler relies on simplifying assumptions about the dynamics of tobacco use and tobacco-related mortality. Importantly, wherever possible, model inputs were based on empirical data, and the model was validated against observed data on mortality in the U.S. (for smoking) and Sweden[22] (for snus use).

[22] This was done in a separate validation exercise (Bachand and Sulsky 2013). The modeling of Camel Snus MRTP effects did not use estimates from the Swedish population; it used U.S.-based smoking mortality statistics, and the specified ERR values to model the effects of snus on mortality, and U.S.-based likelihood of use data to model tobacco use transitions.

The DPM(+1) model estimated survival for a hypothetical male cohort of 1 million individuals and used smoking and mortality data for males as inputs. Extrapolating the model to project effects for a single mixed-gender cohort of males and females is based on analyses that estimate the effect on females to be 19% lower than for males. Input probabilities for tobacco use transitions were not differentiated by gender: the empirically-derived probabilities of primary tobacco use transitions are based on data from the entire mixed-gender sample included in the likelihood of use study, and the arbitrary or extreme inputs for secondary tobacco use transitions also are not gender-specific.

Extrapolation of the single-cohort analyses to estimate the effects on the multiple cohorts that make up the current population implicitly assumes that the inputs (smoking and mortality data, tobacco use transition probabilities) will not vary across age cohorts. It is likely that these parameters do vary. Nevertheless, the analysis provides some insight into the scale of the potential benefit of a Camel Snus MRTP on the different cohorts that make up the current U.S. population aged 13-67.

Many inputs to the DPM(+1) modeler are taken from results of the likelihood of use study, which assessed the interest of various subgroups in purchasing Camel Snus for personal trial. Self-reported purchase intent ratings from the likelihood of use study were translated into purchase probabilities (as a proxy for likelihood of use) using an empirically-validated algorithm. It is likely that these projections over-estimate the adoption of Camel Snus. However, the overestimation is likely to apply across the board, and an overall reduction in the use of Camel Snus reduces both benefits and harms, since both depend on use of Camel Snus, just by different subsets of the cohort (*i.e.*, smokers versus non-smokers). Thus, an overall change in the estimated appeal of Camel Snus is unlikely to change the conclusion that the net effects of an MRTP are positive. Indeed, the DPM(+1) model results show that even reducing all of the estimated transition probabilities by 75% (*i.e.*, simulating an across-the-board decrease in use of Camel Snus) does not change the fundamental conclusion that a Camel Snus MRTP would result in a net benefit to population health.

In another respect, using estimates of use based on the likelihood of use study may underestimate use of Camel Snus. The likelihood of use study results are based on a single exposure to a tobacco company advertisement. Repeated exposures may increase interest in a modified risk tobacco product. This mode of communication may also have limited impact because consumers are skeptical of claims made in advertisements and are particularly suspicious of claims made by a tobacco company (Harris Interactive 2013; Byrne *et al*. 2012). Accurate information about reduced risk of Camel Snus compared to smoking from other, more authoritative, sources may increase the appeal of a modified risk tobacco product, particularly to current smokers not interested in quitting.

The modeling results presented here benefit from considerable strengths. The DPM(+1) considers multiple tobacco use transitions that could affect population health. The DPM(+1) modeler itself and the empirical inputs regarding tobacco use and its effects on survival were

validated against population data for smoking (in the U.S.) and snus use (in Sweden)[23]. The DPM(+1) considers the uncertainty around certain parameters and produces PIs that reflect that uncertainty. The model makes conservative assumptions – for example, by not including the benefits of quitting Camel Snus – suggesting that the benefits may be greater than estimated. The results present only the impact on a single cohort of individuals coming into the age of risk for tobacco initiation. Extrapolations of the model results that consider potential effects on the full population, including those who are already smoking, suggest that the beneficial effects of a Camel Snus MRTP would actually be realized by individuals in all age intervals.

6.4.11 Summary

The DPM(+1), a validated modeler for estimating tobacco-related mortality in a population, was used to assess a diverse set of hypothetical scenarios to consider a spectrum of potential benefits and harms from a Camel Snus MRTP order. The DPM(+1) modeler considers primary tobacco use transitions based on estimates empirically-derived from the likelihood of use study, as well as non-empirical estimates of secondary tobacco use transitions that are considered to be conservative. The Master model considers all of the benefits and harms (with separate adjustment for *Relapse*), while Component analyses estimate the effects of particular tobacco use transitions that are sources of benefit or harm. Besides evaluating scenarios considered to be realistic, tipping point analyses evaluate what percentage of current smokers who were not likely to quit – the intended population for a Camel Snus MRTP – would need to switch to Camel Snus (*Switching*) in order to overcome various conservatively-estimated harms to yield a net positive impact on population health (survival).

Model outcomes are expressed as incremental survival of a single U.S. birth cohort comprised of one million individuals who were 13 years of age at the time of MRTP availability. Following a single cohort that enters the age of tobacco initiation at a time when a Camel Snus MRTP with modified risk advertising is (hypothetically) available yields valid estimates of the effects on that cohort. However, it underestimates the total benefit on the U.S. population, because it does not take into account the potential benefit to individuals already 18 or older at the time of a Camel Snus MRTP introduction, many of whom are already smoking, and thus stand to benefit from *Switching* to Camel Snus. Extrapolations estimate the effect of a Camel Snus MRTP order on the full population, for which a Camel Snus MRTP only becomes available at their current age. Although this exercise is less precise, it is important to consider this potential benefit. Accordingly, it is important to consider the total population benefit, counting both a tobacco naïve cohort from age 13 as well as the multiple cohorts that constitute the current U.S. population aged 18 and older, which includes many adult smokers.

[23] This was done in a separate validation exercise (Bachand and Sulsky 2013). The modeling of Camel Snus MRTP effects did not use estimates from the Swedish population; it used U.S.-based smoking mortality statistics, and the specified ERR values to model the effects of snus on mortality, and U.S.-based likelihood of use data to model tobacco use transitions.

6.4.11.1 Net effects on population health (survival) are likely to be positive and unlikely to be negative

The modeling results consistently indicate that Camel Snus is likely to have a net positive benefit on population health, increasing survival for the population as a whole (*i.e.*, decreasing tobacco-related mortality). The Master model, including empirically-derived estimates of primary tobacco use transitions based on the likelihood of use study and employing a conservative ERR of 0.11, indicates that making a Camel Snus MRTP available with modified risk advertising would increase survival to age 72 by at least 6,000 persons in a single birth cohort of 1 million males that enters its teenage years as the Camel Snus MRTP with modified risk advertising becomes available. Scaling the results to a mixed-gender cohort of 4.1 million individuals indicates that a Camel Snus MRTP would increase survival to age 72 by 23,000 individuals. Considering the full population, which includes adults who are presently smoking, the introduction of the Camel Snus MRTP is estimated to increase survival for individuals in each age interval.

Tipping point analyses using empirically-based estimates of all the potential harmful tobacco use transitions with a Camel Snus MRTP indicate that Camel Snus would offset projected harms if less than 2% of the intended user population (*i.e.*, current smokers who are not likely to quit) switched completely to Camel Snus in each age interval of follow-up. This suggests that having Camel Snus available with MRTP advertising will likely produce a population health benefit, and, moreover, that net population harm is unlikely.

The model uses estimates of the risk reduction due to *Switching* from smoking to Camel Snus that were based on expert estimates. Two estimates were used in these analyses – a 92% reduction in risk (ERR=0.08) and an 89% reduction (ERR=0.11) – and both were modeled with uncertainty. Additionally, a sensitivity analysis using the assumptions included in the Master model, considering all harmful and beneficial tobacco use transitions (after adjustment for *Relapse*), shows that the break-even point where the population is neither benefitted nor harmed, was an ERR of 0.47, or a reduction in risk compared to smoking of 53%. Therefore, even if *Switching* from cigarette smoking to Camel Snus only reduces risk by as little as 50% – much less than the expert estimates of 89%-92% – a Camel Snus MRTP would still have favorable effects on population health.

6.4.11.2 Influence of model inputs on estimated survival

The DPM(+1) outputs demonstrate that the biggest influence on population health and survival is *Switching* – that is, current smokers not likely to quit *Switching* to Camel Snus rather than continuing to smoke. All other tobacco use transitions considered in the model are dwarfed by the beneficial effect of this transition in tobacco use. For example, on its own (without other transitions or harms) empirically-derived rates of *Switching* from the likelihood of use study, applied over the life of the cohort, are estimated to yield an increase in survival of about 48,000-50,000 persons in the 13-year-old mixed-gender birth cohort. In contrast, estimating *Gateway Effect* even as high as 50% (among those who initiated Camel Snus and would not otherwise have used tobacco) results in a net loss to survival of about 4,000 in the birth cohort.

Clearly, the *Gateway Effect* has an adverse impact on population health, and steps should be taken to discourage initiation with Camel Snus and further progression to smoking. The modeling results indicate, however, that at the population level, the positive effect of *Switching* is much greater, and the net effect of Camel Snus availability is positive, even in the face of a *Gateway Effect*.

The reason *Switching* has such a dominant effect on population health is that there are many smokers who are not likely to quit, this large group showed the greatest likelihood of using Camel Snus when presented with modified risk advertising in the likelihood of use study, and continuing smokers have multiple opportunities to engage in *Switching* over their lifetime. Further, the smokers who do switch to Camel Snus stand to gain very significant health benefits, reducing their mortality risk by 89-92% compared to smoking (Levy *et al*. 2004). These factors, in combination, yield very large population health benefits. In contrast, many of the adverse or harmful tobacco use transitions that raise concern about an MRTP apply to much smaller populations and/or to populations that were assessed in the likelihood of use study to have very low likelihood of using Camel Snus. Take *Gateway Effect* as an example. *Gateway Effect* occurs in non-tobacco users who would not otherwise have smoked but take up Camel Snus (the *Additional Initiation* group). The likelihood of use study results indicate that individuals who are not susceptible to smoking also have little interest in trying Camel Snus, suggesting that few of these individuals would adopt Camel Snus. That is why estimating *Gateway Effect* even as high as 50% does not result in large changes in population impact. The same logic applies to beneficial tobacco use transitions such as *Alternative Initiation*, which also occur infrequently, and therefore have minimal impact on net population health.

Parallel analyses were run with two literature-based estimates of risk reduction, an ERR of 0.08 and a more conservative ERR of 0.11. This change made only a modest difference in the estimated population health impact, suggesting that the conclusion that there is a population health benefit does not rest heavily on the precision of the ERR estimate. The modeler also considers the estimates of ERR to be uncertain, and that uncertainty is reflected in the 95% PIs cited in the tables. While the resulting PIs clearly reflect some uncertainty about the magnitude of the benefit of an MRTP for Camel Snus, they do not change the conclusion that there is a benefit. For example, in the Master model using empirically-derived estimates from the likelihood of use study and an ERR of 0.11, the point estimate is 23,394 additional survivors, and the lower bound of the PI is 20,295 survivors per cohort (Table 6.4.9-3) – both reflecting a very substantial population health benefit.

6.4.11.3 Tipping points

Given that *Switching* to Camel Snus is the dominant beneficial tobacco use transition influencing the outcome of the statistical modeling and is the behavior the proposed modified-risk advertisement promotes, tipping point analyses were conducted to assess how much *Switching* is necessary to produce a neutral or beneficial population health impact in the face of extreme estimates of harmful tobacco use transitions. In a Master model using empirically-derived estimates for all primary harmful tobacco use transitions, except *Relapse*, and not

including any other beneficial tobacco use transitions, less than 2% *Switching*, in each age interval of follow-up, is enough to neutralize the potential harmful tobacco use transitions. Estimates based on the likelihood of use study project trial of Camel Snus to be at least this proportion even in the oldest age interval that would benefit from *Switching* and within which the beneficial effect of *Switching* is smallest. As a further context for the 2% rate of *Switching* needed to overcome all the posited harms, the projected *Switching* proportions in the two youngest age intervals where *Switching* could occur (18-22, 23-27), and where *Switching* confers the greatest health benefit, are at least 3 times as great as the *Switching* rate required at the tipping point. Thus, tipping point analyses suggest that achievable rates of *Switching* from smoking to Camel Snus can produce a net benefit in population health (survival).

6.4.11.4 Conclusion: Net population health effects of a Camel Snus MRTP with modified risk advertising are likely to be positive and unlikely to be negative

Modeling the effects with empirically-derived estimates of tobacco use transitions indicate a likely increase of 23,000-25,000 survivors to age 72 for a mixed-gender single birth cohort comprised of non-tobacco-users at age 13. The biggest influence on the net population impact is the proportion of smokers *Switching* to Camel Snus instead of continuing to smoke, reducing their health risks. Even in tipping point analyses that make strongly negative assumptions about rates of harmful tobacco use transitions, a rate of *Switching* of 4% in each age interval of follow-up would neutralize these extreme rates of harmful tobacco use transitions. Moreover, tipping point analyses using more realistic empirically-based estimates of rates of harmful tobacco use transitions based on the likelihood of use study indicate no population harm even if less than 2% *Switching* occurs in each age interval of follow-up. Sensitivity analyses for the risk reduction between Camel Snus and smoking show that a Camel Snus MRTP with modified risk advertising would likely produce a population health benefit even if the risk reduction is only about 50%, rather than the approximately 90% estimated by experts (Levy *et al*. 2004). Thus, extensive modeling of the likely impact of a Camel Snus MRTP demonstrates that marketing of Camel Snus with modified risk advertising is likely to produce a net benefit to population health and is unlikely to result in net negative effects on population health (survival).