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# The *Dynamic Population Modeler (+1)* Used to Show Population Health Benefits Does Not Justify Issuing a MRTP Order for Camel SNUS Products

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## Background

R.J. Reynolds (RJR) is seeking a Modified Risk Tobacco Product (MRTP) order for six Camel SNUS smokeless tobacco products. In order to be granted this order, the FDA must determine that: (1) the product, as actually used, will reduce harm and risk of tobacco related disease to users, and (2) marketing the products as MRTP will have benefits for the health of the population as a whole, including users and non-users of tobacco products.

It is important to recognize that RJR's burden to demonstrate that marketing Camel Snus will benefit for the health of the population as a whole is as essential as the requirement to show that Camel Snus use will significantly reduce harm or the risk of tobacco-related disease. In making its determination, FDA must consider, among other things, the risks and benefits to all persons who may potentially use or be exposed to Camel Snus, and must compare the health risks of Camel Snus to other consumer behaviors, including:

- The health risks associated with use of Camel Snus as compared to using other tobacco products on the market (including other smokeless tobacco or snus products such as Swedish Match snus);
- Changes in health risks to users who switch from using another tobacco product (including e-cigarettes and other kinds of smokeless tobacco such as Swedish snus) to Camel Snus;
- Health risks associated with switching to Camel Snus as compared to quitting the use of tobacco products altogether;
- The health risks associated with using Camel Snus in conjunction with other tobacco products (i.e., "dual use" or "poly use");
- The health risks associated with switching to Camel Snus as compared to using an FDA-approved tobacco cessation medication;
- The health risks associated with initiating use of Camel Snus as compared to never using tobacco products, including potential gateway effects; and
- Risks to non-users, including risks associated with spitting and environmental waste.[1](page 18-19).

In addressing the effect of an MRTP on the population as a whole, FDA recommends that applicants submit quantitative estimates of the effect the proposed marketing may have on population health. These estimates should integrate all the information regarding the marketing of the product and its potential effects on health, tobacco use behavior and tobacco use initiation to assess the effect that product would have on overall tobacco-related morbidity and mortality.[1](pp.

21-22) FDA recommends that applicants quantify the potential changes in morbidity and mortality to the various types of affected individuals in the U.S. population, including:

- Tobacco users who switch from other commercially marketed tobacco products to the proposed product;
- Tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk;
- Tobacco users who opt to use the proposed product rather than cease tobacco use altogether;
- Tobacco users who opt to use the proposed product rather than an FDA-approved tobacco cessation medication;
- Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users;
- Tobacco users who use the product in conjunction with other tobacco products; and
- Non-users who experience health risks from the product.[1] ( p. 22)

In its Guidance, FDA acknowledges the difficulties inherent in making premarket assessments of the effect of marketing a MRTP would have on the population as a whole and the public health, and therefore encourages using statistical models to forecast the population effect and demonstrate an impact on population health.[1](p. 27) For this purpose, RJR uses its Dynamic Population Modeler (DPM) (+1). The model incorporates a number of assumptions, some based on empirical observation and others based on expert opinion or hypothetical use studies with adults. These assumptions determine whether SNUS marketed under a MRTP order will benefit population health or not.

The DPM is described in section 2.13 *Statistical Modeling of the Effects on the Health of the Population as a Whole* of the Executive Summary. We reviewed this model both in terms of the reasonableness of the assumptions as well as whether it satisfies FDA requirements for MRTP orders.

**Assessment of the DPM (+1)**

- **RJR describes the model as a "fit-for-purpose statistical modeler"** (section 2.13.1, page 221).
    - It follows a cohort of males with no tobacco use at age 13 through age 72.
    - The model compares a base-case in which only cigarettes are smoked to a counterfactual case that includes use of Camel SNUS marketed as an MRTP.
    - The sole outcome considered is survival (mortality).
    - The net benefit to the population is primarily through the effect of snus use on smoking cessation among current cigarette smokers who would otherwise not have quit smoking.

- **The model only considers mortality, despite the fact that tobacco use (including snus) causes considerable morbidity**
    - Models are based on males, but projections are adjusted for male vs female differences taking into account lower survival benefits for females (19% less than males), different smoking rates, and actual population numbers for males and females for 2005 (Executive Summary, 2.13.3, pp. 234-235).

- RJR asserts that "tipping points" would be similar but does not provide specific evidence to support this assumption
- Scenarios consider mortality from lung cancer, oral cancer, respiratory disease, and heart disease. No other cancers are considered, and the diseases included in the respiratory and heart disease categories are not clearly defined.
- The model defines population health as "survival" (p. 233, 2.13.3). No measures of morbidity are included.
- The cohort is modeled from age 13-72. Stopping at 72 misses most mortality, which occurs after that. It may be that "premature mortality" is defined as occurring before 72 but this is not clearly stated.
- By excluding morbidity and mortality after age 72, the model likely underestimates the adverse population effects of approving the MRTP application.

- **Dual/poly users are assumed to have the same risk as cigarette smokers**
  - The potential additive effect of using multiple products is not considered
  - Dual use of smokeless tobacco (ST) products (including SNUS) and other products is common. According to an analysis of the 2012-14 National Adult Tobacco Survey,[2] 3.6% of U.S. adults aged 18+ were current ST users (See Table 1 of the cited paper). Among these current ST users, 52.4% of them concurrently used one or more other tobacco products.
  - By ignoring the additive risk of using both SNUS and other tobacco products, the impact on population health is likely underestimated

- **The model was validated but the data used for validation are problematic**
  - The base case for the US was validated using 1980 smoking initiation (Substance Abuse and Mental Health Services Administration 1999, full citation not provided) and cessation rates (RJR cites Messer et al. 2007, but does not provide the full citation). They found the rates to be within .2% of the actual age-specific survival probabilities estimated using the 2006 U.S. life table (Arias 2010, full citation not provided) (page 223).
    - More recent life tables for the US are available.[3] Newer life tables would reflect lower mortality rates due to reduced smoking prevalence and other lifestyle interventions.
  - The counterfactual case was validated using Swedish male data on the use of snus (Lundqvist et al. 2009, full citation not provided). The predicted estimates of mortality were within 0.3% of the actual age-specific survival probabilities estimated using the 2006 Swedish life table. However, Swedish data may differ from the US because:
    - Swedish input parameters are very likely different from US input parameters
    - Swedish SNUS have lower nitrosamine levels than the SNUS sold in the US and would thus be likely to result in lower mortality rates.
  - By overestimating mortality in the base case and underestimating mortality in the counterfactual case, the model is biased towards a higher reduction in mortality compared to the counterfactual case.

- **The model does not use the most recent data on smoking initiation/cessation**.
    - On Page 243 of the Executive Summary, RJR indicated that both their multiple cohort full population analysis model and the single-cohort analysis model used the 2000 mortality rates, the 2009 smoking initiation rates, and 2005-2008 smoking cessation rates. However, they did not provide the data sources for these parameters. There are newer available data for all these measures.
    - Given the substantial declining trend in cigarette smoking in recent years, these data are likely to overestimate cigarette initiation and underestimate cessation, leading to an overly positive impact of SNUS compared to cigarettes.

- **Tobacco use transitions are based on RJR research with "large groups of adults" to ask likelihood of use**
    - This is described in Section 6.3 of the application which as of August 15, 2018 was not publicly available, precluding evaluation of the valididity of the values that RJR uses in its model.
    - These findings were converted into estimated probabilities of use using a previously developed algorithm (Section 2.13.2.1). The reference for this algorithm is not provided so there is no way to assess its validity.
    - Transitions among different tobacco use categories are critical parameters in the DPM (+1), but the rates used cannot be fully assessed due to lack of information.

- **The model assumes that switching rates (from cigarette to SNUS use) are much greater than additional initiation rates (from never tobacco users to SNUS use) under MRTP marketing (page 232)**

    - The assumed probability of "switching to snus use" among current cigarette smokers who otherwise would have continued smoking was:
        - 14.2%-16.5% for smokers aged 18-62
        - 1.7%-3.1% for smokers aged 63-72
        - Assumed no switching would occur before age 18
        - These switching rates are higher than those reported elsewhere. One randomized controlled trial found that while 82% of smokers offered free SNUS tried the product, only 4% were using SNUS after 12 months.[4] This study also found that SNUS users were less likely to attempt to quit smoking and did not smoke fewer cigarettes per day.
    - The probability of "additional initiation" of snus use among never tobacco users is merely 0.3%
    - Thus, the "switching" probability is 47-fold or 55-fold higher than the "additional initiation" probability.
    - It is the high switching rate compared to the low initiation rates that is primarily responsible for the net positive impact on population health (page 235).
    - These assumptions bias the model toward finding a positive impact of approving the MRTP application on population health.

- **Diversion from quitting is considered in the model to decline with age**
    - The model assumes an increase in population harm resulting from the "diversion from quitting" of cigarette smokers who would have quit but instead switch to Camel

SNUS. This effect declines with age. Rates are based on the likelihood of use studies for those who had engaged in quitting behaviors and expressed interest in SNUS (Executive Summary, 2.13.2.1.2.2, page 233). Rates of those who would have quit but instead use SNUS are:
    - 8.6 – 20.0% for smokers aged 18-22
    - 1.6-2.2% for smokers aged 68-72
  - The model that is scaled for a mixed gender cohort shows that diversion from quitting results in an additional 900-1700 deaths, and 4,400 – 7,300 if some of those who switch to SNUS instead of quitting relapse to cigarette smoking (Executive Summary, Table 2.13.3-2, page 238).
  - Because these estimates are based on likelihood of use studies rather than empirical data, it is difficult to judge their veracity.

- **Gateway effects are considered but assumed to be small**
  - The models assume that half of the snus initiators would become cigarette smokers (i.e., gateway effect), but this estimate is based on a very low probability of never tobacco users transitioning to initiate snus use - .3% in each age interval (see Figure 2.13.2-1, page 229 and Section 2.13.2.1.2.1, page 231)
  - There is limited data on SNUS initiators who do not use other tobacco products
    - A 2012 telephone survey of 3,627 US adults found that .1% used SNUS alone[5]
    - A recent analysis of the Population Assessment of Tobacco and Health (PATH) data found that 1.0% of youth had ever used smokeless tobacco only (including SNUS) in 2013-14. These youth were 1.5 to 4.3 times as likely to be using cigarettes a year later depending on what covariates were controlled in the model,[6] a much larger effect that RJR assumes.
  - The low rate of SNUS initiators is consistent with available evidence, but the rate of transitioning to cigarette smoking is low compared to empirical evidence, so the negative impact of the gateway effect is probably underestimated in the model.

- **The Excess Relative Risk (ERR) of smoking vs SNUS assumption is critical**
  - The model assumes SNUS is 11% as risky as smoking for 35-49 year olds and 8.2% as risky for those aged 50 and older, based on comparing long-term SNUS users and long-term cigarette smokers. This excess relative risk estimate is based on the opinions of a nine-person panel of experts who were asked to estimate mortality risks associated with long-term use of low-nitrosamine smokeless tobacco after reviewing the available published scientific literature as of 2003.[7]
    - A Delphi approach was used via e-mail to obtain estimates for the 2 age groups for lung cancer, heart disease, and oral cancer. Three rounds were conducted to reach a convergence. Estimates differed substantially by disease category, but an adjusted mean value was used for total mortality.
    - Using an adjusted mean value across disease categories increases the excess relative risk used for lung cancer and reduces the excess relative risk used for oral cancer. For heart disease, the category likely to be responsible for the largest number of deaths, the RJR model uses the mean values of 11.0% and 8.2% for the 2 age groups compared to the values the experts estimated of 10.8% and 11.1%. Using a lower excess relative risk for older tobacco users

may introduce a substantial bias in mortality estimates toward underestimating the effects.

- The low-nitrosamine product considered reflects Swedish SNUS. However, US SNUS uses tobacco with higher nitrosamine levels, so this is not an accurate comparison.
- This key model parameter is not based on any observed data
- Section 6.4 apparently does sensitivity analyses, but this section was not available to review as of August 15, 2018.
- Tipping point analysis (essentially a breakeven analysis) looks at what percent of smokers would have to switch to SNUS to offset adverse effects. Based on the assumption of SNUS being .08-.11 times as harmful, only 2% would need to switch for a net benefit.
- Sensitivity analyses re the tipping point for excess relative risk found that as long as the ERR was less than 46-48% that of cigarettes, the effect on population health is net positive (Page 242, Section 2.13.3.3.1).
  - This statement is true only if all the other assumptions for the main model remain unchanged, including the very low "additional initiation" probability of 0.3%. If the "additional initiation" probability is indeed 30-fold or 40-fold higher, the results of break-even relative risk would be much lower than 46%-48%.
  - The analysis does not compare the effects of SNUS with e-cigarettes or other forms of smokeless tobacco
- The estimates of the excess relative risk are quite low and not based on empirical evidence.
- If the estimates of excess relative risk were more realistic or if the excess relative risk of SNUS were compared with a lower risk tobacco product such as e-cigarettes, there would be a more negative impact on population health.

- **RJR acknowledges that they omit the possibility that SNUS use may delay smoking cessation**
  - The impact of including this in the model would be to reduce the benefit of marketing SNUS as an MRTP by increasing smoking-attributable mortality.

- **Contrary to FDA guidance, RJR ignores morbidity**
  - FDA guidelines state that scientific studies submitted by the applicant "should contain an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality (page 21).[1]
  - RJR does not include any measures of morbidity, including tobacco-caused disease incidence or tobacco-attributable healthcare costs. For cigarettes, morbidity is much greater than mortality: in the US, 6.9 million adults reported smoking-related diseases in 2009[8] while smoking causes 500,000 deaths a year.[9]
  - Wang et al.[10] found that smokeless tobacco use, including chew, snuff, and SNUS, accounted for over $3.4 billion in excess annual healthcare expenditures, including $1.8 billion for hospitalizations. $0.7 billion for emergency room visits, and $0.9 billion for doctor visits (2014 dollars). While this study was not able to separately estimate costs attributable to SNUS use, the findings suggest that these costs could be substantial.

- Ignoring disease morbidity resulting from SNUS use underestimates its impact on health and medical costs.

- **The model does not consider people who may switch from e-cigarettes to SNUS**
  - No attempt is made to model potential initiation among users of other tobacco products, such as e-cigarettes.
  - The model only considers people who initiate with cigarettes or SNUS, but many young people initiate with e-cigarettes.
  - Because e-cigarettes are likely to have a lower mortality risk than cigarettes, the excess relative risk of SNUS vs. e-cigarettes may be positive or negative, and switching from e-cigarettes to SNUS would have a very low or possibly negative population health effect.

- **The model does not include the impact of SNUS on non-users of tobacco products**
  - Potential health risks from SNUS to non-users, such as infections from exposure to expectorate or environmental waste are not considered.
  - Insofar as SNUS impacts cigarette smoking, such as a gateway effect leading to smoking or reducing smoking cessation, the model needs to consider the impact of secondhand smoke on non-smokers.
  - Omitting the impact of SNUS use on non-tobacco users will lead to an underestimation of the harm to the population of marketing SNUS as an MRTP.

- **Sensitivity analyses are designed to favor a positive impact on population health of a SNUS MRTP order**
  - The base of the assumed "additional initiation" probability is very low (i.e., at 0.3%). Thus reducing it by 75%in the sensitivity analyses leads to almost zero initiation probability (i.e., 0.075%).
  - For the "switching" probability, the 75% reduction of 14.2%-16.5% leads to a new level of 3.55%-4.15%, which is still about 47-fold or 55-fold higher than the "additional initiation" transition probability.
  - A more realistic assumption for sensitivity analyses would be to increase the "additional initiation" probability by at least 20-fold or 30-fold to the level of 6.0% or 9%. In this way, the results shown in Table 2.13.3-1 for the population-level harmful effect under "additional initiation" and "additional initiation with Gateway Effect" would be much larger in terms of absolute magnitude.
  - Sensitivity analyses are conducted on a number of parameters, but these are varied one at a time, and no attempt is made to compare the cases where all parameters are at their extreme values.
  - As conducted, the sensitivity analyses are biased in favor of a positive impact of SNUS on population health.

**Summary**

The DPM (+1) structure is detailed and comprehensive as far as it goes, but it leaves out important elements, such as youth initiation and relationships with tobacco products other than cigarettes. More important, there are problems with the values of the parameters assumed in the

model and with omissions. These problems with the parameters in the model bias the results in favor of concluding a population benefit for SNUS.

Excess relative risk is a crucial parameter but is based on an older study reporting expert opinion and a comparison of lower nitrosamine Swedish SNUS to cigarettes. The transition rates in the model, including never tobacco-user to smoker or SNUS user, cigarette smoker to SNUS user or dual cigarette/SNUS user, and cigarette smoker to SNUS user to non-tobacco user are based on use studies – self-reported likelihood of use. Built into the model is the assumption that switching rates from cigarettes to SNUS will far exceed additional initiation rates of non-tobacco users. These assumptions all bias the results to show a population health benefit from SNUS marketing as an MRTP.

The model also omits a number of components that the FDA requires be included in assessing the benefit or harm of issuing an MRTP order. Morbidity is not measured in any way. Health risks to non-users of SNUS are not included but might include not only exposure to SNUS expectorate or product waste but also any increase in secondhand smoke exposure resulting from increased cigarette smoking related to SNUS use.

The DPM (+1) considers only cigarette use and ignores the possibility of SNUS users who switch from other tobacco products. E-cigarette use is increasingly popular and if e-cigarette users switch to SNUS, the excess relative risk would be much lower, possibly negative. Evidence suggests that many SNUS users will be dual or poly users. The DPM (+1) also omits any additional risk for dual users, assuming their mortality risk is the same as smokers.

RJR conducted sensitivity and tipping point analyses, but these analyses do not vary parameters across the full meaningful range of values and vary only one parameter at a time, which will lead to an underestimate of the true range of possible outcomes.

The DPM (+1) is biased in favor of finding a population health benefit for marketing SNUS as a MRTP. For the reasons outlined above, the FDA should not rely on the model as presented and should not grant a MRTP order for Camel SNUS products.

**References**

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