Modeling the Population Health Impact of Flavor Variety and Potential Risk of Youth Initiation Resulting from the Marketing of an Oral Nicotine Pouch Product

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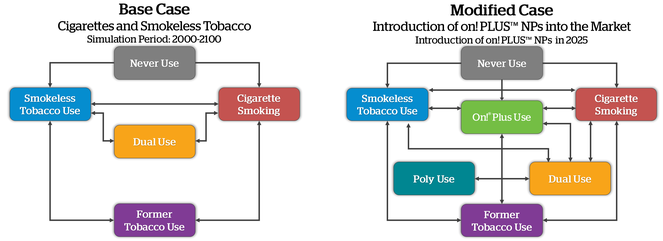
Abstract

on! PLUS™ products are new oral tobacco-derived nicotine pouch products (NP) that have reduced Harmful and Potentially Harmful Constituents (HPHCs) and offer an alternative for adults who use smokeless tobacco (ST) products. A marketing determination of a new product by the FDA considers the risks of nonuser initiation against the benefit of users switching to a potentially lower risk product.
We used a validated agent-based model[1] to evaluate the impact of marketing the NPs and the contribution of non-tobacco flavor varieties on morbidity and mortality in the U.S. population. Importantly, we assessed the risk to youth using tipping point analyses to predict their hypothetical initiation rates that would offset any benefit from switching by adults who use ST.
Simulated marketing of the NPs resulted in a benefit to the population with a 0.40 percentage point reduction in ST prevalence and prevention of 74,000 premature deaths over a 75-year period. Limiting the NP portfolio to tobacco flavored products reduced the projected benefit by 73%. Tipping point analyses indicated that youth (ages 12-17) initiation rates specific to these NPs would have to increase more than 40 times from 0.04% and 0.03% to over 1.64% and 1.23% for males and females, respectively, resulting in underage prevalence more than 3.46% before the population benefit would reduce to zero. While no youth should use tobacco, prevalence trends approaching this level may provide early signals of population health risks.
Understanding the role of flavors and the risk to youth is important in regulatory decision-making. While all models have limitations, these simulations provide a methodology for quantifying the risks of potential initiation vs the benefit of switching to potentially lower risk products, including benefits associated with flavored products.

Introduction

on! PLUS™ nicotine pouch (NP) products are an oral tobacco-derived nicotine pouch intended for adults who use smokeless tobacco (ST). Switching completely to NP products with low or non-quantifiable levels of HPHCs may present a potential to reduce harm among adults who use ST. Non-tobacco flavored NPs may play an important role in facilitating switching since a majority of adults who use ST products use non-tobacco flavored ST. FDA authorization to market new tobacco products in the U.S. requires applicants to provide scientific evidence demonstrating such products are appropriate for the protection of public health (APPH). Part of demonstrating APPH requires assessing the potential impact of marketing a new product on youth use.
Modeling is one tool that can be used to assess the risks and benefits to the population as a whole resulting from the introduction of new products into the market. Importantly modeling can be used to test extreme scenarios to understand how initiation of underage individuals has potential to offset any benefits from adults switching and to evaluate the impact of non-tobacco flavor varieties.

Modeling Framework



The impact on the population as a whole is determined based on the difference in tobacco use prevalence and all-cause mortality (premature deaths prevented) between the Base and Modified Case scenarios

Conclusion

- Modeling indicates market authorization of on! PLUS™ NPs will have a positive population health benefit.
- Limiting the NP portfolio to only tobacco flavor reduces the population benefit to 20,000 premature deaths prevented, a 73% reduction compared to 74,000 predicted in the Modified Case when non-tobacco flavors are included.
- Tipping point sensitivity analyses demonstrate low risk to underage populations.

References

1. Muhammad-Kah, R., et al., *A computational model assessing population impact of a new tobacco product.* Qeios, 2023.
2. Friedman, G., Tekawa, I., Sadler, M., & Sidney, S. (1997). Smoking and mortality: The Kaiser Permanente experience. In D. Shopland, D. Burns, L. Garfinkel, & J. Samet (Eds.), Changes in cigarette-related disease risks and their implication for prevention and control. : U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute.
3. Fisher, M.T.; Tan-Torres, S.M.; Gaworski, C.L.; Black, R.A.; Sarkar, M., (2019) Smokeless tobacco mortality risks: An analysis of two contemporary nationally representative longitudinal mortality studies. Harm Reduct. J. 16;27
4. Nutt et. al. (2014) Estimating the Harms of Nicotine-Containing Products Using the multi-criteria decision analysis (MCDA) Approach. Eur Addict Res, 20:218–225.
5. Hyland, A., et al., *Design and methods of the Population Assessment of Tobacco and Health (PATH) Study.* Tob Control, 2017. **26**(4): p. 371-378.

Modeling provides an objective method to quantify the population impact of nicotine pouch products to support the regulatory determination of whether these products are appropriate for the protection of public health.

Methods

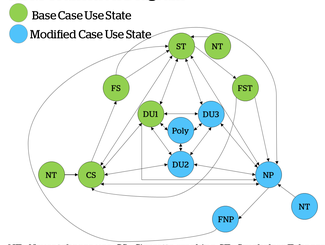
Agent-Based Model (ABM)

- The model is initialized with a hypothetical population of 2.81MM agents, (1/100th of U.S. population in the year 2000 by age, gender, & tobacco use status)
- At each 1 yr. time step:
  - Survivability of agents evaluated based on mortality risk factors depended on tobacco use history
  - Agents who survive, transition between use states
  - New agents are introduced due to birth & immigration

Mortality Risk Factors

- NT, CS, and FS - Derived from Kaiser Permanente data[2] adjusted for U.S. mortality rates in the year 2000.
- ST - Excess Relative Risk (ERR) of ST use compared to smoking set to 0.09[3].
- NP - Excess Relative Risk (ERR) of on! PLUS™ NPs use compared to smoking set to 0.05. Conservative compared to 0.02 value determined by Nutt et al for oral nicotine-containing products[4].
- Dual and Poly Use – Set as the higher risk product.

ABM Transition Diagram



NT= Never tobacco use, CS= Cigarette smoking, ST= Smokeless Tobacco Use, FS= Former Cigarette Smoking, FST= Former Smokeless Tobacco Use , DU1= CS + ST, NP= Nicotine Pouch Use, FNP= Former Nicotine Pouch Use, DU2= CS + NP, DU3= ST + NP, Poly= CS+ ST+ NP

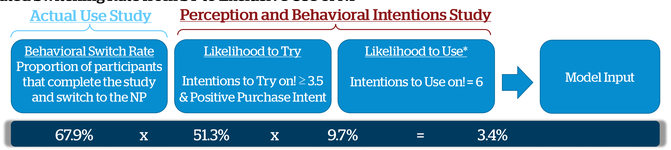
Base Case Transition Sources

- CISNET estimated probabilities for cigarette initiation and cessation
  - The cessation rates in CISNET are based on at least two years of successful smoking cessation, therefore relapse from FS to CS state is set to zero.
- Transition probabilities between cigarette smoking and smokeless tobacco (ST) use were estimated from PATH[5] Wave 1 and Wave 2 data among never snus users stratified by three age groups (12-17, 18-24 & 25-64).

Modified Case Transition Sources

- Product specific transition rates were estimated from two internal studies:
  - Perception and Behavioral Intentions Study (PBIS) – Online survey of 3,015 adults including tobacco users and non-users
  - Actual Use Study (AUS) - 6-week ad libitum Actual Use Study which included 1,219 adults who used dip or snuff (including those who did and did not smoke cigarettes).
- Transition probabilities not estimated from our internal studies were estimated from PATH Wave 1 and Wave 2 data using snus transition data as estimates for NP
- Transition from exclusive adult smoking to exclusive NP use is set to zero to ensure model predictions of premature deaths prevented are not overstated, due to the larger difference in all-cause mortality risk between combustible cigarettes and the NP products and provides more focus of the population impact resulting from transitions related to smokeless tobacco product use.

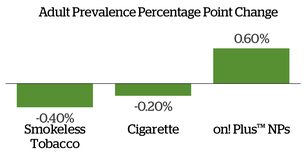
Estimated Switching Rate from ST to Exclusive Use of NP



Likelihood to Use = Among those who were likely to try that have the highest intentions to use (i.e., post-exposure composite score equal to 6) and positive purchase intent

Results

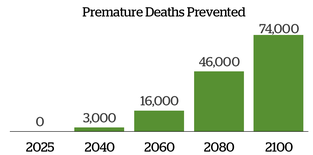
Population Health Impact



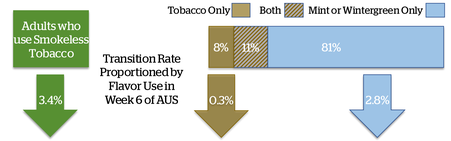
Modeling Predicts

- **Reduction** in ST prevalence by 0.40% pts
- **Prevention** of 74,000 premature deaths

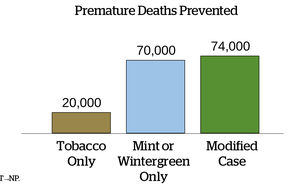
Over 75 years with the inclusion of on! PLUS™ NPs



Impact of Flavor Variety

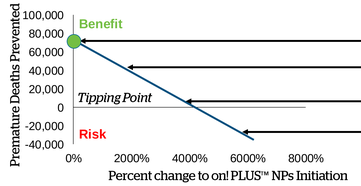


Transitions adjusted based on flavor use in Week 6 of the AUS: ST →NP; ST →ST+NP; CS+ST →Poly; CS+ST →ST+NP; CS+ST →CS+NP; CS+ST →NP. Initiation of NP among NT was set to zero in the Tobacco only scenario. All other transitions remain the same as in the Modified Case



Limiting the NP portfolio to only tobacco flavor reduces the population benefit to 20,000 premature deaths prevented

Tipping Point Analysis



on! PLUS™ NPs Initiation Rate Percent Change from the Modified Case**	*on!* PLUS™ NPs Initiation Rate Inputs by Age Range and Sex				Premature Deaths Prevented by 2100	*on!* PLUS™ NPs Prevalence in year 2100
	12-17		18-20			
	Male	Female	Male	Female		
0 (Modified Case)	0.04%	0.03%	0.05%	0.03%	74,000	0.16%
2000%	0.84%	0.63%	1.05%	0.63%	58,000	1.85%
4000%	1.64%	1.23%	2.05%	1.23%	6,000	3.46%
6000%	2.44%	1.83%	3.05%	1.83%	-25,000	5.01%

While no youth should use any tobacco product, tipping point scenarios illustrate that on! PLUS™ NPs specific initiation rates for underage never user populations would have to rise well beyond those currently observed for the entire cigarette (0.5%†) and smokeless tobacco (0.14%†) categories to result in a net risk to the population as a whole.

†ALCS analysis of PATH W5-W6 current use of tobacco products among youth never users of e-cigarettes, cigarettes and smokeless tobacco ** All other transitions remain the same as in the Modified Case

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