Assessing the population health impact of authorizing the marketing of a smokeless tobacco product with a proposed modified risk claim

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PMTA / MRTPA Requirements (§ 910/911)

Section 910 - Premarket Tobacco Product Application (PMTA) - New Tobacco Products*

Demonstrate that… "…is appropriate for the **protection of the public health** shall be determined with respect to the **risks and benefits to the population as a whole.**"

* http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm262073.htm

Section 911(g)(1) - Modified Risk Tobacco Products (MRTP) - Reduced Risk

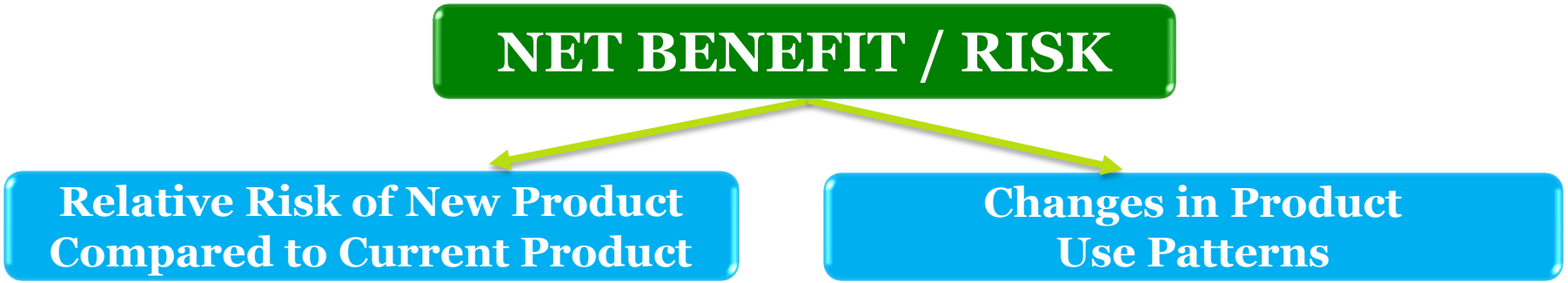
Demonstrate that a MRTP as used by the consumers will:

A. Significantly **reduce the risk and harm of tobacco-related disease** to the tobacco user.

B. Secondly it should benefit the **health of the population as a whole**, taking into account both users of tobacco products and persons who do not currently use tobacco products

Population Health Standard

- Assessing impact on population as a whole including users and non-users



Population modeling can be used to estimate the combined impact of both components

*FDA's Draft Guidance for Industry Modified Risk Tobacco Product Applications . http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf

Population Models - New Tobacco Products

- Several population models have been developed, such as:
  - RAIS (Bachand & Sulsky, 2013)
  - PMI (Weitkunat et al., 2015)
  - BAT (Hill & Camacho, 2017)
  - JT (Poland & Teischinger, 2017)
  - FDA CTP/Sandia Lab (Vurgin et al., 2015)
  - Warner & Mendez (2018)
  - Levy et al. (2018)
  - Cherng et al. (2016)
- ALCS has developed two population models:
  - ALCS Agent-based Model (ABM)
  - ALCS Cohort Model

Illustration of the ALCS Cohort Model

Evaluating Impact of Authorizing a Modified Risk Claim for a Product Currently on the U.S. Market

USSTC submitted MRTPA for Copenhagen Snuff Fine Cut on March 20, 2018

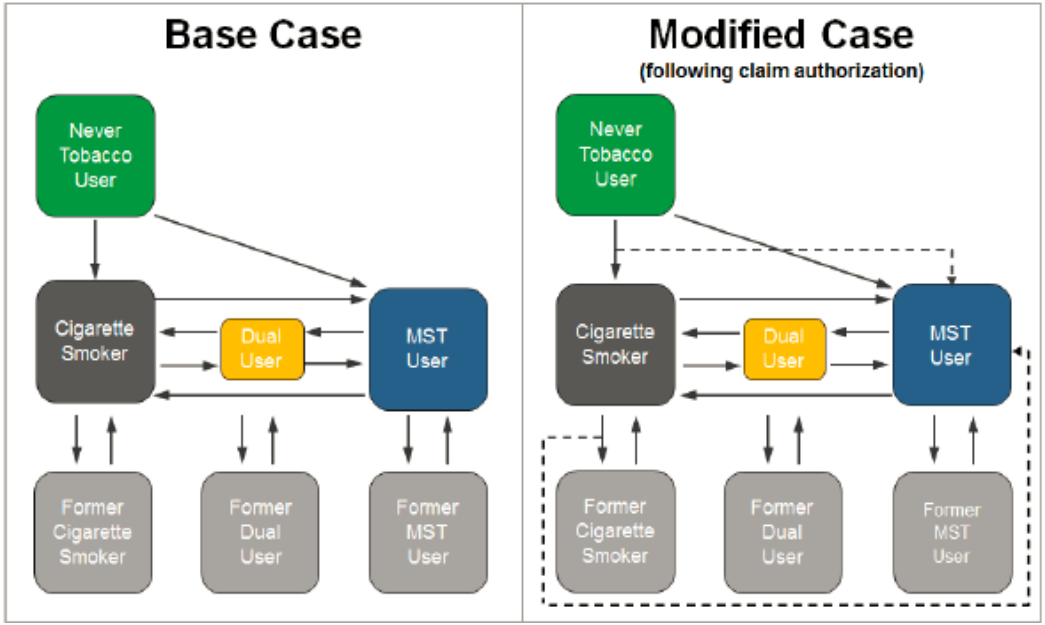
Accepted and filed for scientific review by FDA on Sept. 14, 2018

MRTPA = Modified Risk Tobacco Product Application
USSTC = U.S. Smokeless Tobacco Company

Modeling Framework: Evaluating Impact of MRTP Authorization

Compare difference in *All-cause Mortality* between Base Case (Status Quo) and Modified Case

Both cigarettes and MST products co-exist in the U.S. market



A future state where both cigarettes and MST products co-exist in the U.S. market, but MST is authorized to be labeled as an MRTP

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ALCS Cohort Model

- Consists of two interlinked sub-models:
  - Transition Sub-model
  - Mortality Sub-model

- Can be employed in:
  - Single Cohort Format*
  - Multiple Cohort Format - Population Level estimates

* The single cohort model is similar in structure to the model shared in Bachand AM and Sulsky SI (2013) A dynamic population model for estimating all-cause mortality due to lifetime exposure history. Regulatory Toxicology and Pharmacology. Volume 67, p. 246-251.

Inputs and Assumptions

Mortality Sub-model

- Never Tobacco Users, Smokers and Former Smokers Mortality:
  - Developed from analysis of the 60,000 cohort sample based “Smoking and Mortality: The Kaiser-Permanente (KP) Experience” study*
  - Adjusted KP data to reflect U.S. population of Yr. 2000
  - Built Poisson models based on age, gender, years smoked, years quit and interaction terms
- MST Users and Former MST Users Mortality:
  - Excess Relative Risk (ERR) of MST use compared to smoking derived from analysis of the NHIS mortality linkage public use data
- Dual Use assigned same mortality risk as that of cigarette smoking

* Friedman G, Tekawa IS, Sadler M and Sidney S (1997). Smoking and Mortality: the Kaiser Permanente Experience. In Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. Shopland DR, Burns DM, Garfinkel L and Samet J, eds. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute. p 477-499.

Excess Relative Risk (ERR) based on Hazard Ratios (HR)

- HR for all-cause mortality developed from ALCS Linked Mortality Analysis*

Never User HR=1

Current ST HR=1.10

Current Smoker HR=2.12

- ERR estimate for Smokeless Tobacco User compared to Cigarette Smoker

$$ERR_{MSTCS} = \frac{HR_{MST} - 1}{HR_{CS} - 1} = \frac{1.10 - 1}{2.12 - 1} = 0.09$$

*HR estimates from the publicly available NHIS dataset were used as we wanted others in public health to be able to replicate our analysis. The publicly available HR estimates were slightly different from the restricted dataset; however, we believe that this will not impact the model outcomes significantly, since we conducted a sensitivity analysis using a wider range of ERR values.

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HR = Hazard Ratios
ST = Smokeless Tobacco

Inputs and Assumptions

Transition Sub-model

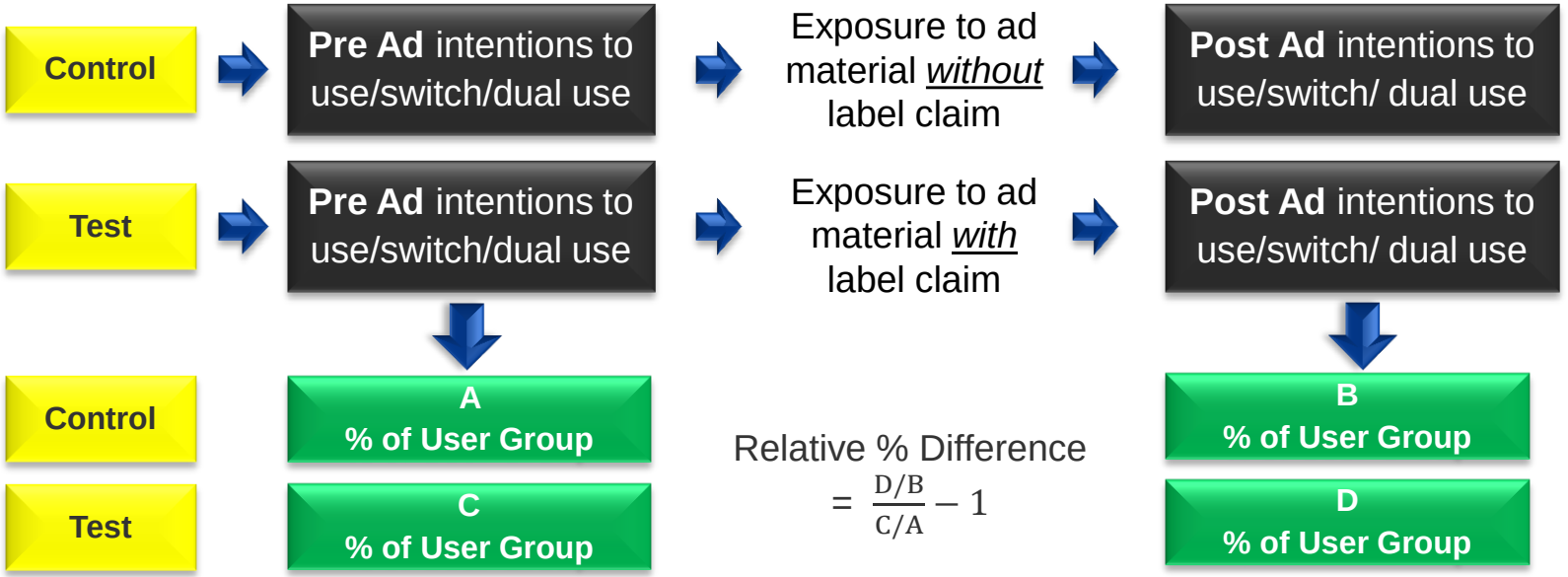
- Base Case Transition Rates:

  Nationally representative transition probabilities estimated from Tam et al. (2015)*

- Modified Case Transition Rates:
  - Study Title: Claim Comprehension & Intentions Study
  - Population Sampled: tobacco users and never-users
    - N = 5871 participants
  - Design: Pretest Posttest Control Group
  - Model inputs derived from Behavioral Intentions and Purchase Intent data
    - Intention metrics developed in accordance with FDA guidance and standards in psychometrics^

*A systematic review of transitions between cigarette and smokeless tobacco product use in the United States. Tam et al. BMC Public Health (2015) 15:258.
^AERA, APA, & NCME. (2014). Standards for educational and psychological testing. Washington, DC: American Educational Research Association.
^FDA. (2009). Guidance of industry: Patient-reported outcome measures: Use in medical product development to support labeling claims.: Retrieved from https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf.

Model Inputs from Claim Comprehension & Intentions Study (CCIS)



- Estimate relative percent difference between response of Test and Control group
- Applied the estimated relative percent differences to Base Case transition rates to generate the Modified Case transition rates

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Modified Case Transition Rates from ALCS CCIS

Tobacco Use Transition	Base Case Transition Rates from Tam et al.	Relative percent difference between response of Test and Control group in CCIS	Transition Rates Modified by CCIS
Never User of tobacco initiating MST candidate product *(Initiation)*	1.6%	-4.8%	1.5%
Former MST Users initiating MST candidate product	1.7%	0%	1.7%
Current Cigarette Smokers switching to MST candidate product *(Switching)*	1.4%	20.8%	1.7%
Current Cigarette Smokers switching to *Dual Use* (MST candidate Product & cigarettes)	3.2%	24%	4.0%
Dual Users (MST and cigarette) switching to MST candidate product	17.4%	5.7%	18.4%
Would-be smoker initiating MST candidate product	-	-	1%
Would-be smoking quitter switching to MST candidate product	-	-	5%

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CCIS = Claim Comprehension & Intentions Study
Candidate Product = MST with Label Claim

Results: 1MM Male Single Cohort

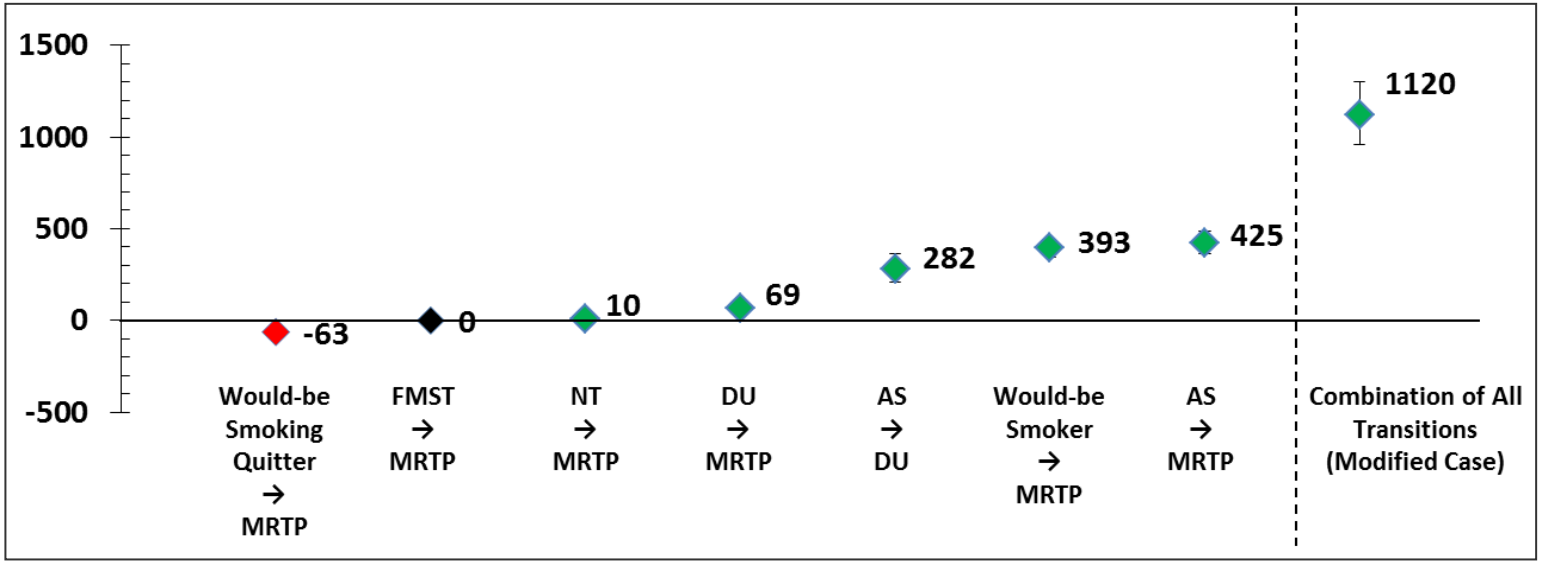
Comparison of Survivors in the Base Case versus Modified Case

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

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

1,120 premature deaths prevented with 32,856 additional years of expected life, for a one-million male cohort followed from age 13 to age 73

Results: Understanding Impact of Individual Transitions



Transitioning of cigarette smokers to exclusive MST use and/or dual use contribute significantly to the overall benefit

Dual User = Current cigarette smoker and MST user; MRTP = MST marketed with a modified risk claim. Mean difference in number of survivors in a one million male cohort between the Base and Modified Case Scenarios: Point Estimates and Credible Intervals for 7 transitions of interest (Component Analysis).

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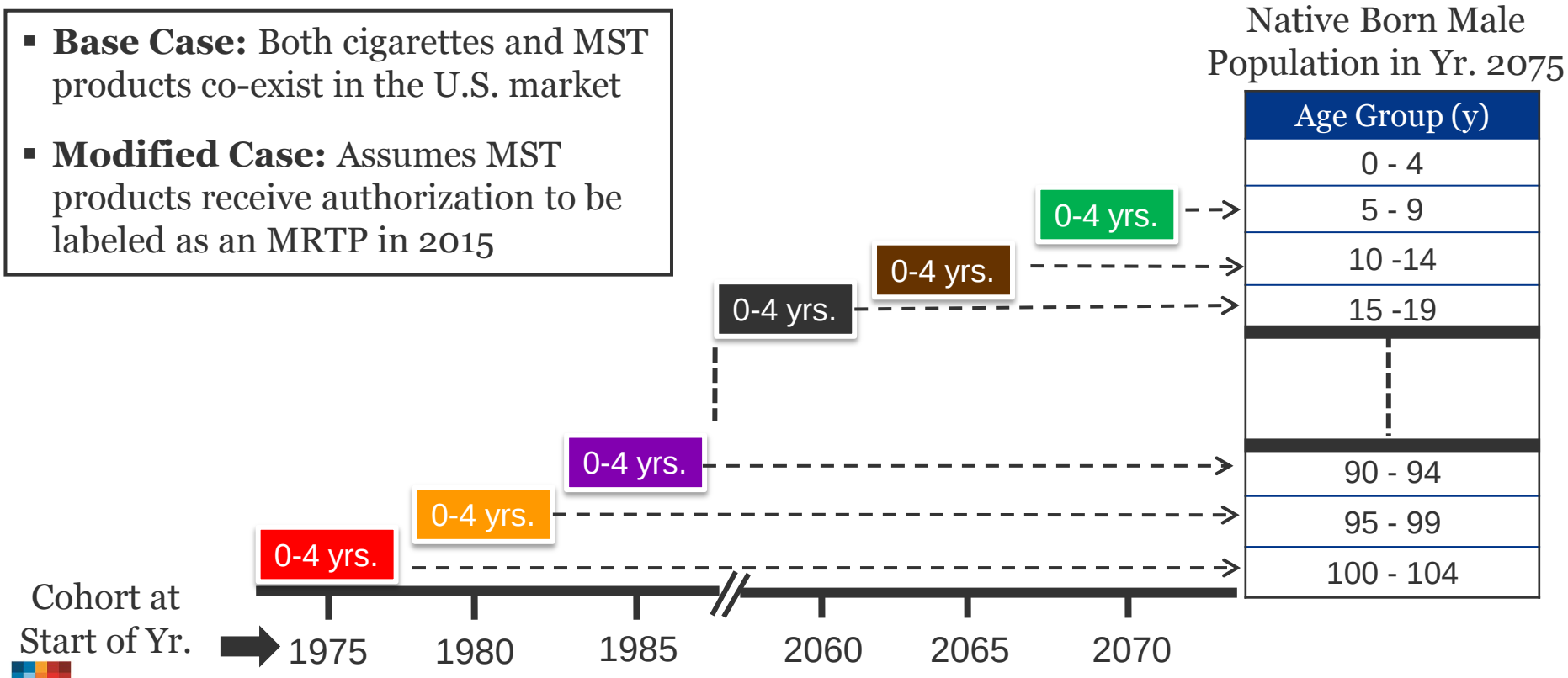
Multiple Cohort Approach - Population Level Estimates

- **Base Case:** Both cigarettes and MST products co-exist in the U.S. market
- **Modified Case:** Assumes MST products receive authorization to be labeled as an MRTP in 2015



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Results: Multiple Cohort Setting - Population Level Estimates

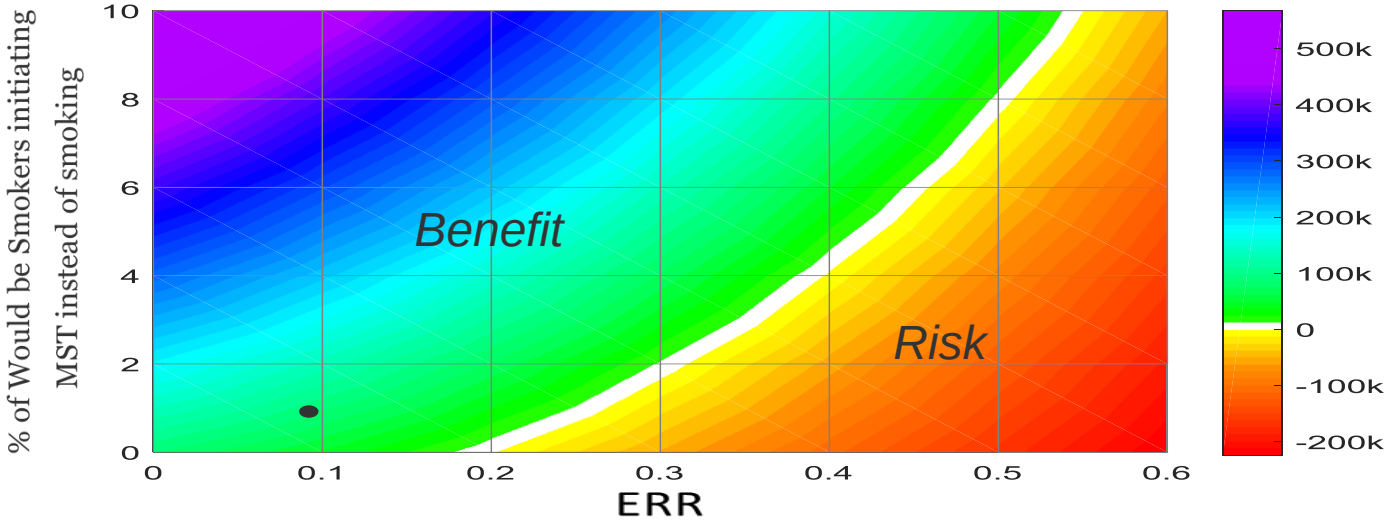
Difference in the Number of Survivors Between the Modified and Base Case

Age Group (y)	Difference in number of survivors in 2075
10-14	0
15-19	0
20-24	0
25-29	153
30-34	473
35-39	973
40-44	1,920
45-49	3,731
50-54	6,788
55-59	9,771
60-64	12,307
65-69	14,813
70-74	15,614
75-79	14,470
80-84	12,310
Total Additional Survivors in the Modified vs. Base Case	**93,323**

- Model predicts ~ **93,000** premature deaths will be prevented over a 60-year period, following authorization to market MST with a label claim
- The premature deaths prevented from market authorization of the *candidate product* with the proposed claim can be estimated by scaling the category level estimates of premature prevented deaths , using *its current market share*
  - *Current U.S. Market share of Candidate Product = 8%*
  - *Net benefit attributable to Candidate product = 93,000* 0.08 = ~**7500***

Output Maps Example - *Risk/Benefit Sensitivity Analysis*

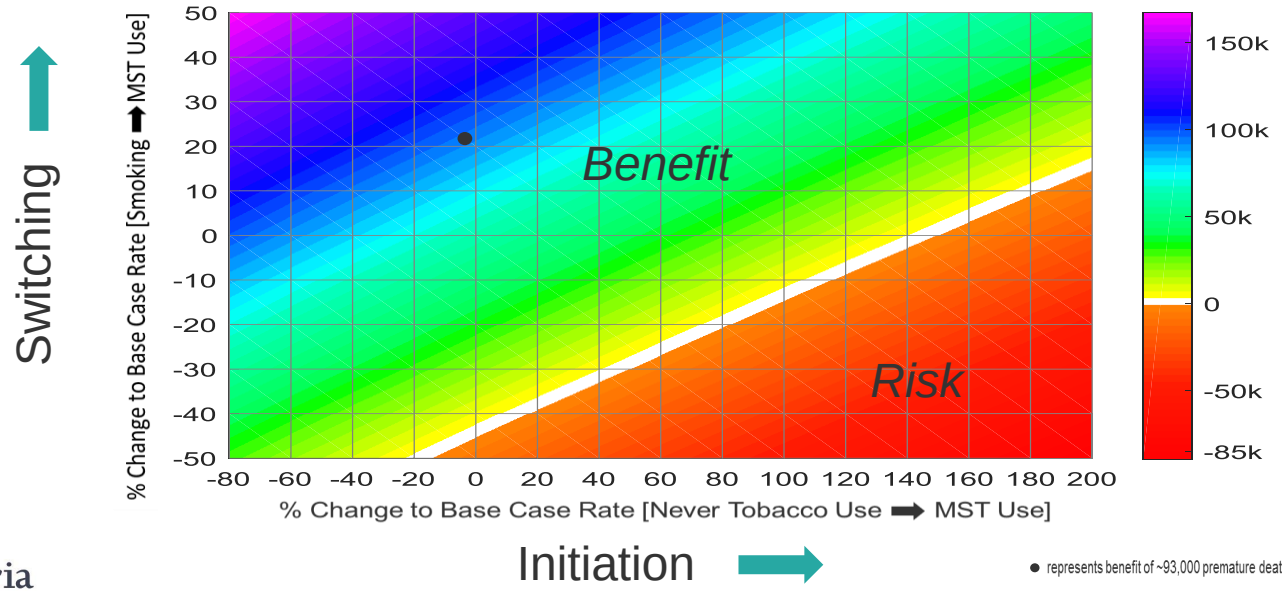
- Concurrently vary:
  - Risk: Increasing ERR
  - Benefit: % of Would be Smokers initiating MST instead of smoking
- All other transition rates kept the same as those in the Modified Case scenario



● represents benefit of ~93,000 premature deaths prevented over a 60-year period, as observed in the Modified Case Scenario

Output Maps Example - *Risk/Benefit Sensitivity Analysis*

- Concurrently vary:
  - Risk: Change in rate of Never Tobacco Users initiating on MST *(Initiation)*
  - Benefit: Change in rate of Cigarette Smokers switching to MST *(Switching)*
- All other transition rates kept the same as those in the Modified Case scenario



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Limitations

- Assumption that product-specific initiation, cessation, and other transition rates do not change over the modeling time period
- Models do not currently estimate morbidity
- Relative percent change in intentions is used as a proxy for relative percent change in behavior
- Our models do not take into account any potential major changes in smoking prevalence due to unforeseen external factors

Summary

- We developed the ALCS Cohort Model using well-established best modeling practices and tested it using uncertainty and sensitivity analyses

- Modeling results indicates that FDA authorization of the proposed modified risk claim yields a modest net health benefit to the population as a whole. Further, model estimates do not indicate unintended consequences that negate this benefit.

Thank You

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Advertising with the Proposed Modified Risk Claim

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Epidemiological Data Sources for Relative Risk Estimates

- *ALCS Linked Mortality Analysis*

National Health Interview Survey

- Survey Years: 1987 – 2005 (intermittent)
- **~155,000** total respondents
  - **~3,000** smokeless tobacco users

National Longitudinal Mortality Study

- Based on the Current Population Survey
- Survey years: 1993-2005
- **~231,000** total respondents
  - **~3,500** smokeless tobacco users

Two nationally representative public health surveys linked to the National Death Index (2011 update)*

*Mortality outcomes available through linkage to the National Death Index (NDI) available from the National Center for Health Statistics

Harm Reduction Opportunities - Smokeless Tobacco

Based on ALCS analysis of PATH Wave 1 data [Sep 12, 2013 – Dec 14, 2014]

Modeling Good Research Practices*

- Right amount of complexity to allow for informed decision making
- Clearly defining assumptions
- Using validation and sensitivity analysis to ensure that outcomes are reasonable
- Systematic identification and justification for use of best available data sources

Products on the Market

- Nationally representative longitudinal or cross-sectional studies
- National databases (PATH, NHIS, NSDUH, etc.)

New Products or Products with a Claim

- Claim comprehension and intentions studies (CCIS)
- Actual use studies (AUS)

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PATH = Population Assessment of Tobacco and Health
NHIS = National Health Interview Survey
NSDUH = National Survey on Drug Use and Health

*Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM), Joint Modeling Good Research Practices Task Force