

# Tobacco Harm Reduction

## E-Vapor Products

Michael Fisher, Ph.D.  
June 8, 2018

1<sup>st</sup> Scientific Summit on Tobacco Harm Reduction



**Altria**

Altria Client Services

# Cigarette Smoking: A Significant Public Health Problem

Cigarette smoking causes about **one of every five deaths** annually in the U.S

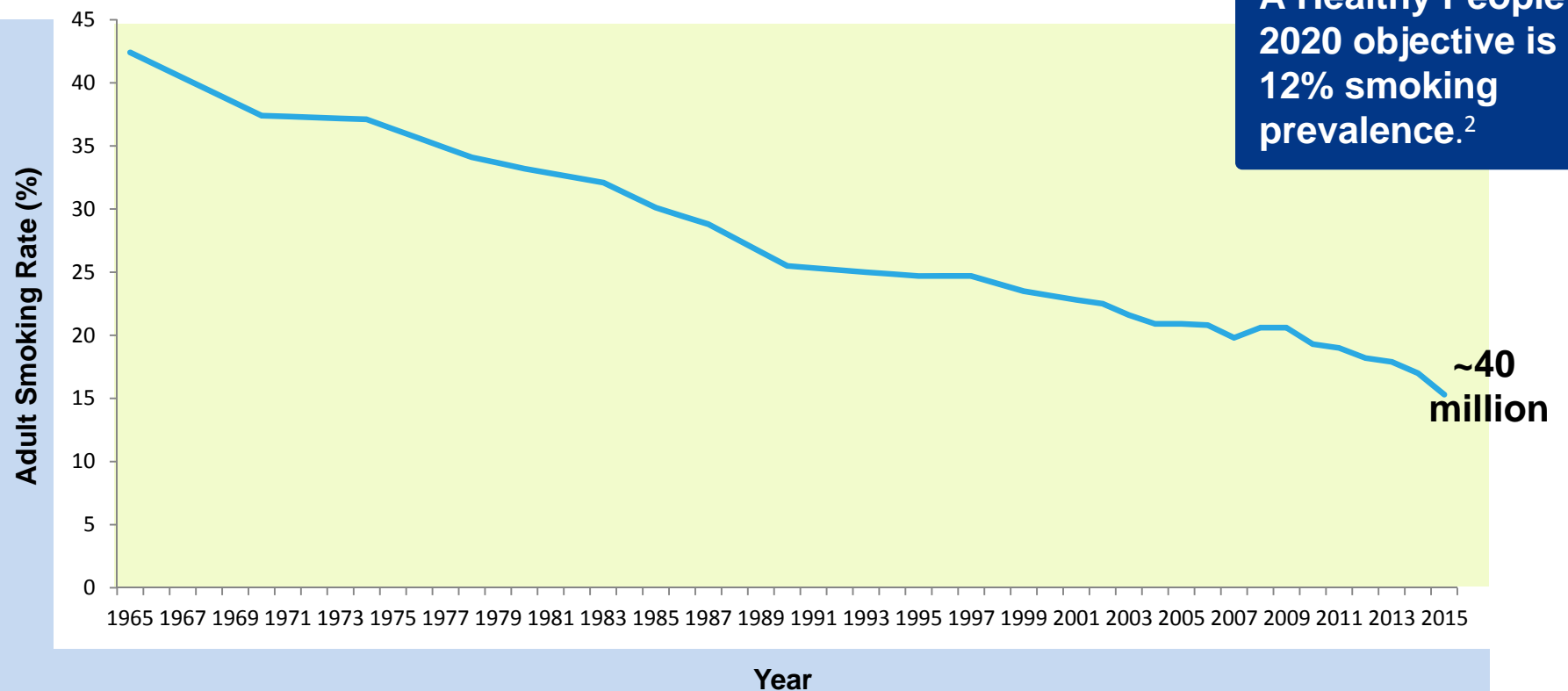
Cigarette smoking causes an estimated **480,000 deaths** annually.

**Smokers' life expectancy** is about **10 years shorter** than nonsmokers'

Source: [http://www.cdc.gov/tobacco/data\\_statistics/fact\\_sheets/health\\_effects/tobacco\\_related\\_mortality/index.htm#cigs](http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm#cigs)



# Cigarette Smoking Trends Among U.S. Adults 1965 – 2015<sup>1</sup>



<sup>1</sup> [http://www.cdc.gov/tobacco/data\\_statistics/tables/trends/cig\\_smoking/index.htm](http://www.cdc.gov/tobacco/data_statistics/tables/trends/cig_smoking/index.htm)

<sup>2</sup> <https://www.healthypeople.gov/>



# FDA Recognizes Continuum of Risk

*“We must recognize the potential for innovation to lead to less harmful products, which, under FDA’s oversight, could be part of a solution. While there’s still much research to be done on these products and the risks that they may pose, they may also present benefits that we must consider.”*

Dr. Scott Gottlieb  
FDA Commissioner

## Continuum of Risk

Combusted Tobacco Products

Non-combusted Tobacco Products

MOST  
HARMFUL

LEAST  
HARMFUL

July 28, 2017: Protecting American Families: Comprehensive Approach to Nicotine and Tobacco  
<https://www.fda.gov/NewsEvents/Speeches/ucm569024.htm>



# Tobacco Harm Reduction at Altria



**Continuum of Risk**

**Combusted Tobacco Products**

**Non-combusted Tobacco Products**

**MOST  
HARMFUL**

**LEAST  
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**Altria**

July 28, 2017: Protecting American Families: Comprehensive Approach to Nicotine and Tobacco  
<https://www.fda.gov/NewsEvents/Speeches/ucm569024.htm>

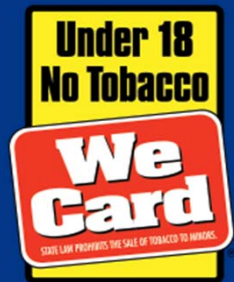
Altria Client Services | Regulatory Affairs | 1<sup>st</sup> Scientific Summit on Tobacco Harm Reduction | June 8 2018 | Final | 5

# Altria Supports Harm Reduction in a Variety of Ways

**Developing &  
Marketing  
Lower-Risk  
Tobacco  
Products**



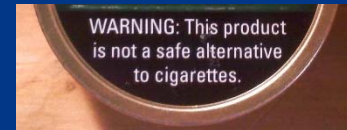
**Help Reduce  
Underage  
Tobacco Use**



**Supporting  
Cessation**



**Communicating  
about the health  
effects of  
tobacco use**





# Harm Reduction Opportunities



\*Source: 18+ATCT 12MM ending December 2017  
Numbers may not foot due to rounding



# Noncombustible Tobacco Product Platforms

## E-Vapor



## Oral Tobacco/ Nicotine Products



## Heated Tobacco Products

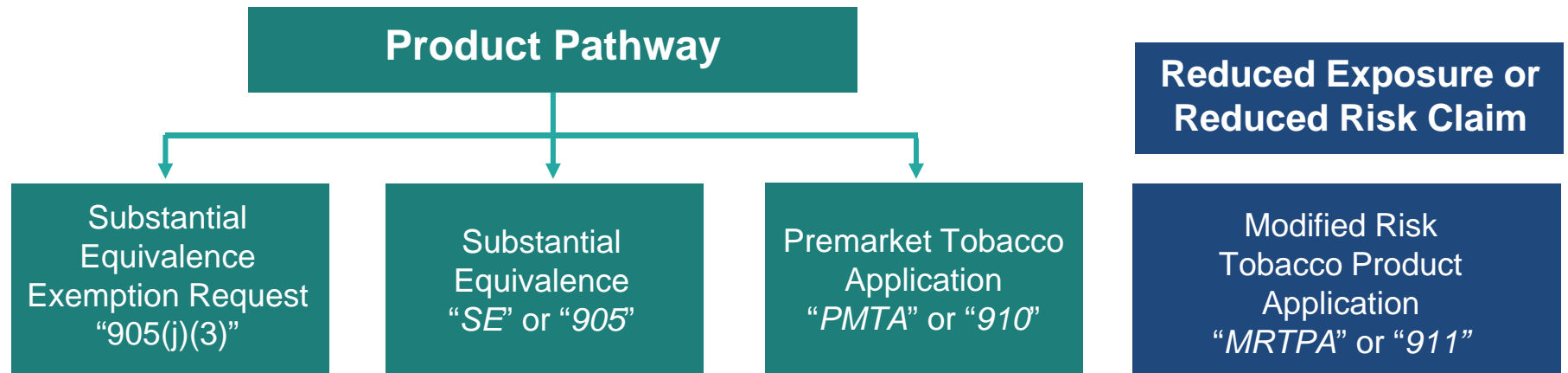




# Diverse E-vapor Product Portfolio



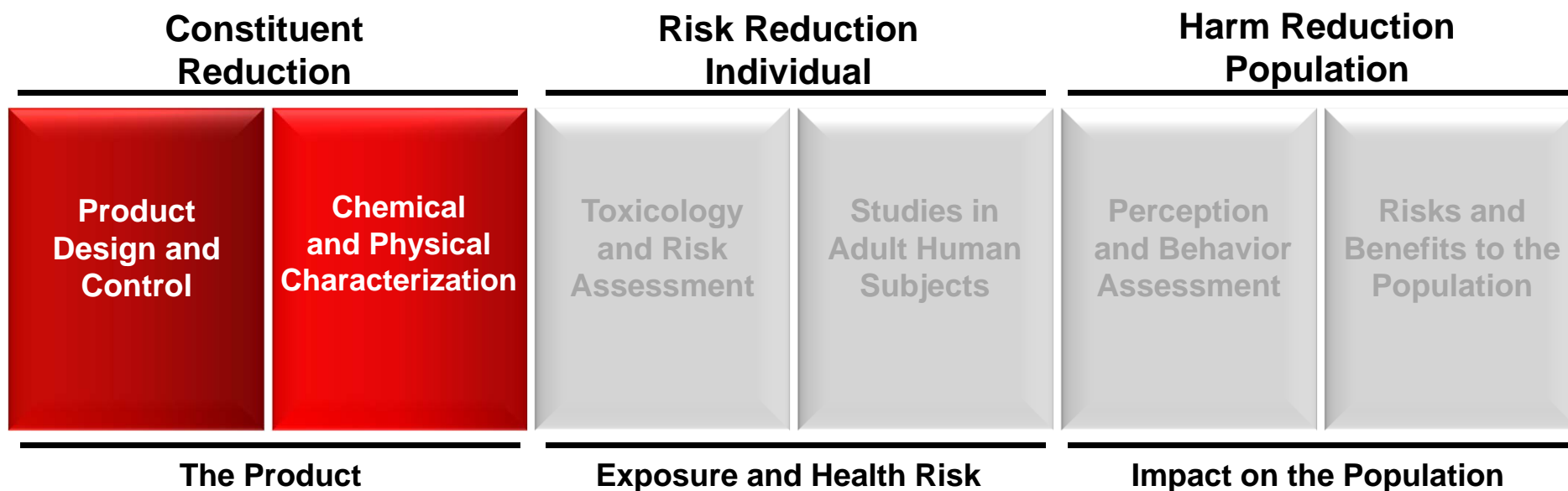
# FDA Market Pathways



# ALCS Framework for Reduced Harm Tobacco Products



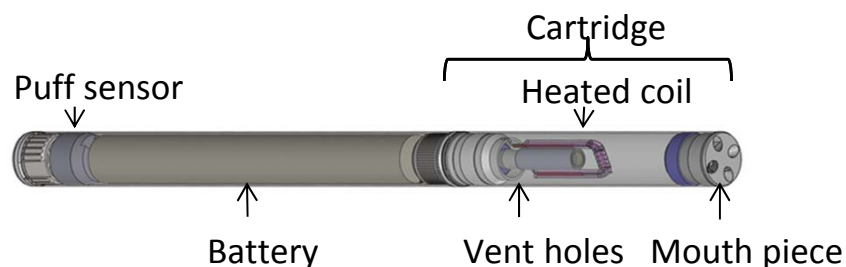
# ALCS Framework for Reduced Harm Tobacco Products



# MarkTen<sup>®</sup> Product was Designed to Eliminate or Significantly Reduce HPHC<sup>1</sup> Generation

Product Design  
and Control

Chemical  
and Physical  
Characterization



## 1 Product Design and Controls

- Selection and evaluation of individual components and ingredients
- Manufacturing standards and quality controls
- Product stability
- Battery safety

## 2 Chemical and Physical Characterization

- Elimination or reduced formation
- Selected HPHC
- Other targeted constituents (e.g. metals)

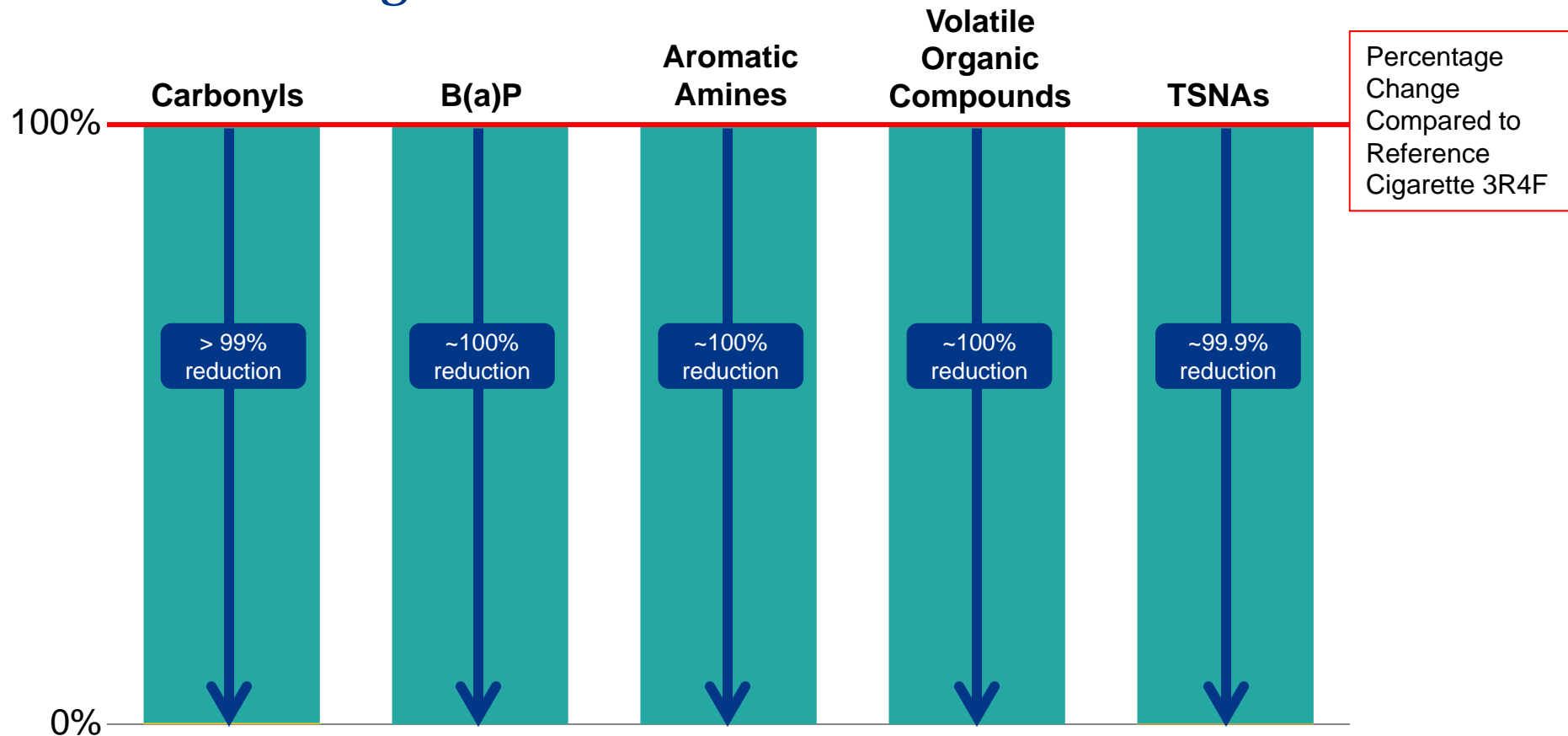
<sup>1</sup> HPHC = Harmful or Potentially Harmful Constituents





# Harmful and Potentially Harmful Constituents in MarkTen<sup>®</sup> Aerosol Are Substantially Lower Than Reference Cigarettes

Chemical  
and Physical  
Characterization



ALCS Internal Report LIQUID 16241 – MarkTen<sup>®</sup> XL Classic 3.5% nicotine, Official Stability Study – PMT1, 3, 6 and 9 months. Average of 140 intense puffs (55mL, 5 second duration, 30 second inter-puff interval).

# ALCS Framework for Reduced Harm Tobacco Products



# Reduced Risk Assessment: Pre-Clinical Studies

Toxicology  
and Risk  
Assessment

## 1 Ingredients risk assessment

Toxicological literature review

Flavors and carriers are:

- Generally recognized as safe (GRAS) for use in foods
- Food or pharmaceutical grade

## 2 Carrier assessment

## 3 Flavor assessment

90 day in-vivo studies

## 4 E-liquid and aerosol condensate

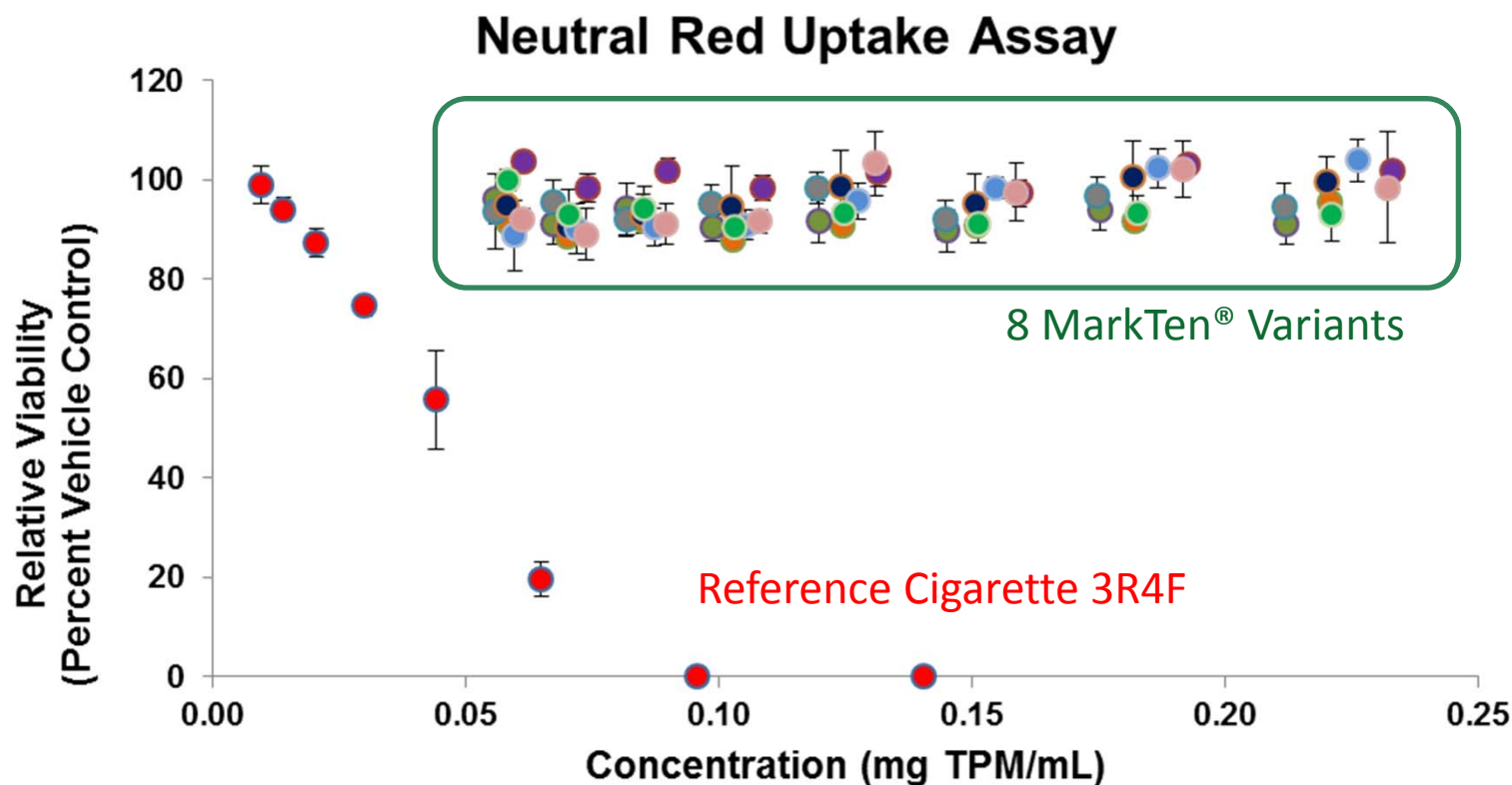
In-vitro toxicology studies

- OECD guidelines
- Cytotoxicity and genotoxicity



# No Cytotoxicity Observed from MarkTen<sup>®</sup> Aerosol Condensates in Neutral Red Uptake Assays<sup>1</sup>

Toxicology  
and Risk  
Assessment

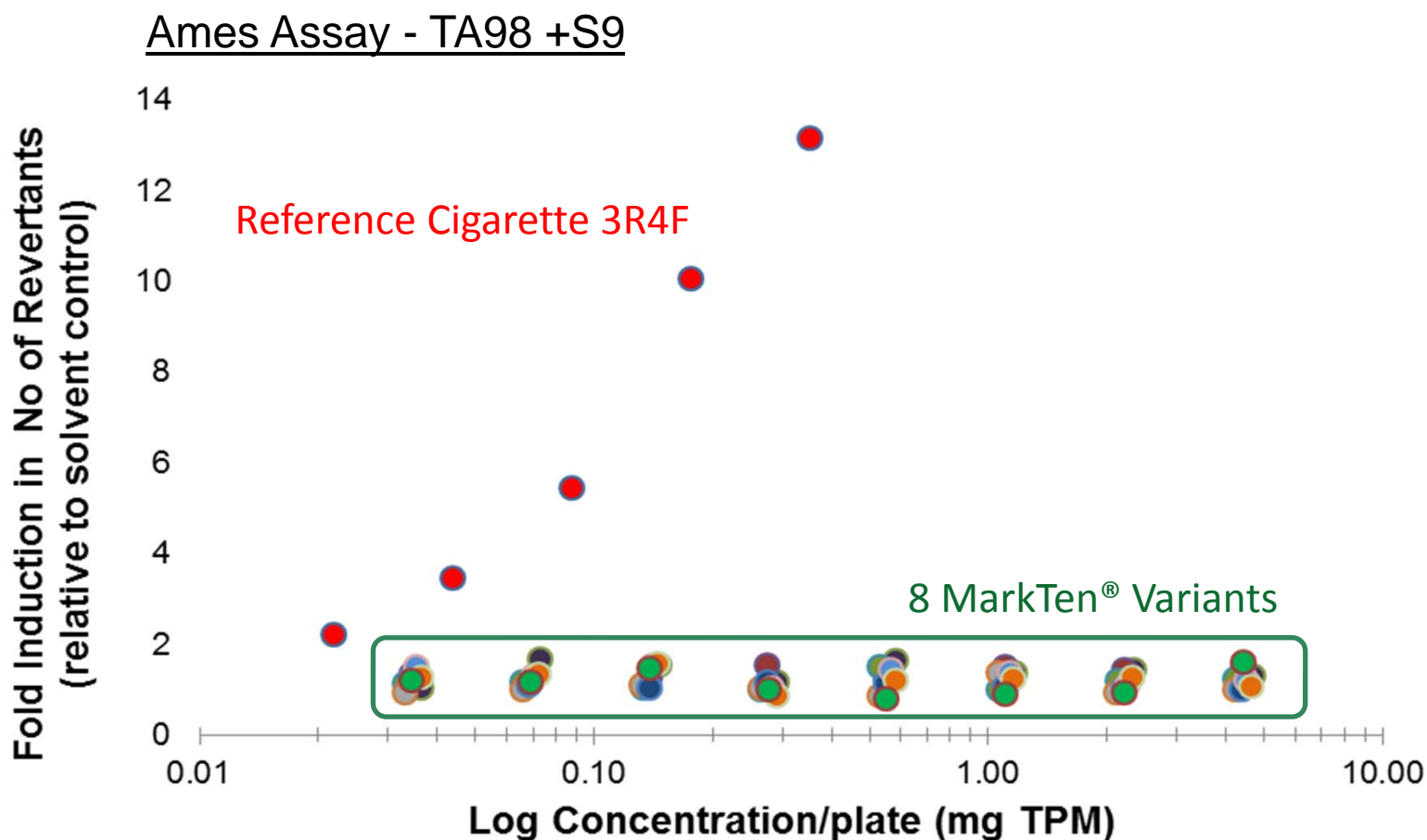


- The 3R4F condensate: Positive response(IC50 of 0.048 ±0.004 mg/mL TPM)
- E-vapor condensates: Viability > 80% (IC50 could not be estimated)



<sup>1</sup> Data shared at Society of Toxicology 2018 Annual Meeting. Doshi et al., Comparison of in vitro Cytotoxicity and Genotoxicity of Condensates Derived from E-vapor Products and Combustible Cigarettes.

# No Mutagenicity Response Observed from MarkTen<sup>®</sup> Aerosol Condensates in Ames Test<sup>1</sup>



<sup>1</sup> Data shared at Society of Toxicology 2018 Annual Meeting. Doshi et al., Comparison of in vitro Cytotoxicity and Genotoxicity of Condensates Derived from E-vapor Products and Combustible Cigarettes.



# Reduced Risk Assessment: Pre-Clinical Studies

Toxicology  
and Risk  
Assessment

## Key Takeaways:

1 Ingredients risk assessment

2 Carrier assessment

3 Flavor assessment

No treatment related effects

- Survival
- Body weight
- Clinical observations & chemistry parameters
- Histopathology

4 E-liquid and aerosol condensate

No evidence of mutagenicity or cytotoxicity



# ALCS Framework for Reduced Harm Tobacco Products



# MarkTen® Users Have Lower Levels of Biomarkers of Exposure and Potential Harm

Studies in Adult  
Human Subjects

1 Pharmacokinetics/  
Pharmacodynamics

Nicotine delivery and satisfaction

2 Reduced Exposure 3-months

Exposure reduction assessment (in progress)

3 Reduced Risk 6-months

Biomarkers of potential harm (in progress)

4 Cross-sectional category study

Exposure and risk assessment

5 Second hand vapor

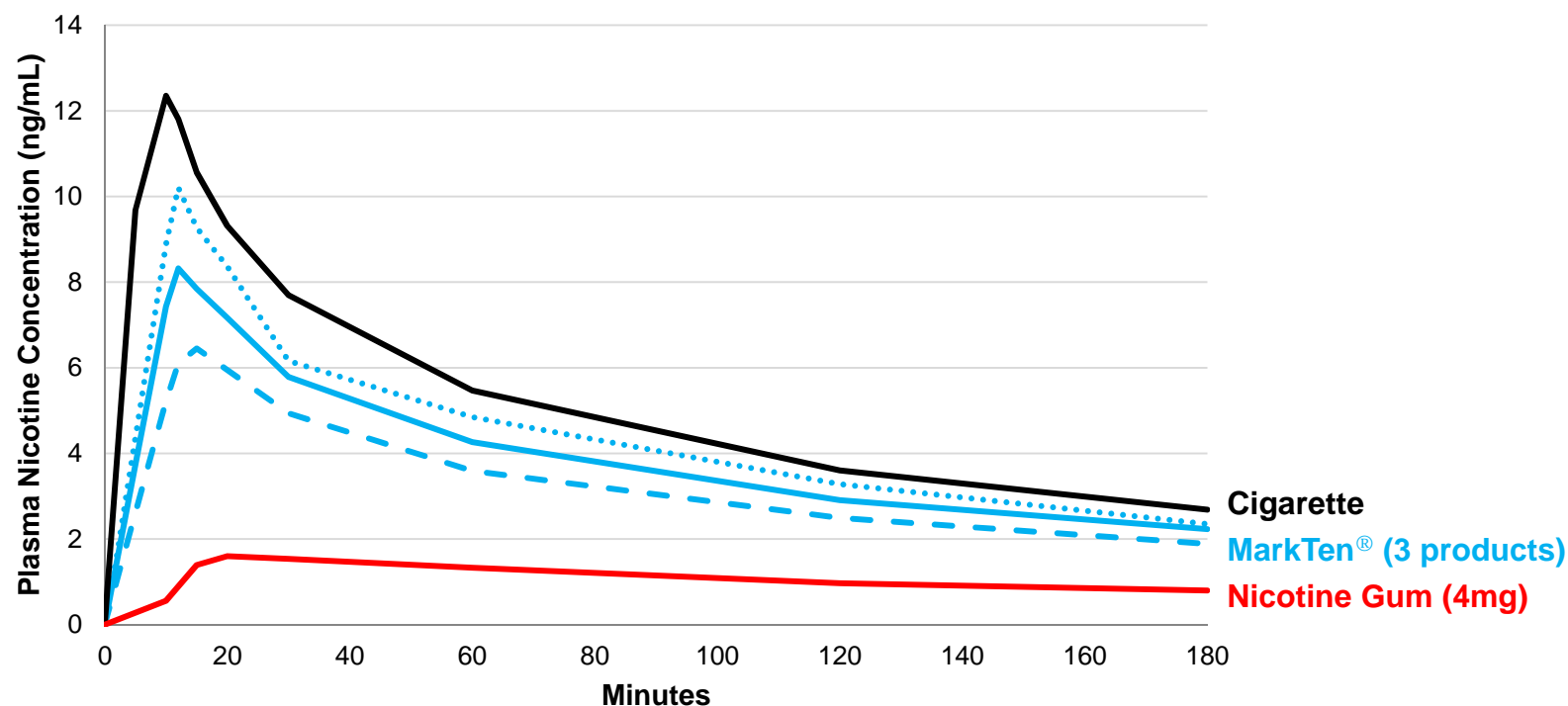
Impact on non-users

Results have been shared at the Global Forum on Nicotine, Society for Research on Nicotine and Tobacco, Tobacco Science Research Conference and other scientific meetings. Abstracts and presentations of these data can be found on our science website [www.altria.com/alcs-science](http://www.altria.com/alcs-science).



# MarkTen<sup>®</sup> Nicotine Pharmacokinetic Studies Demonstrate a Range of Nicotine Deliveries<sup>1</sup>

Studies in Adult Human Subjects

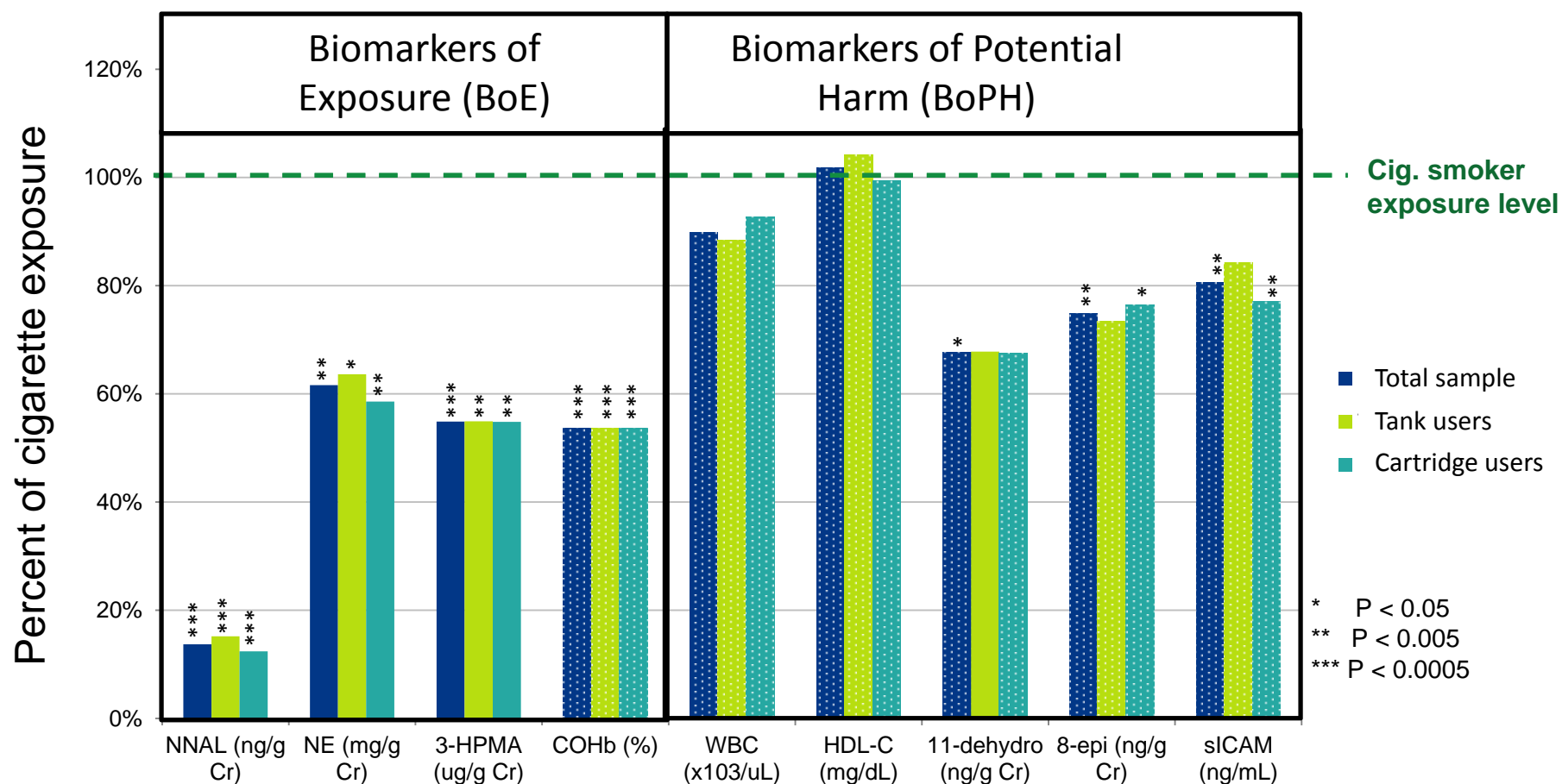


<sup>1</sup> Data shared at Society for Research on Nicotine and Tobacco 2018 Annual Meeting. Oliveri et al., Characterization of Nicotine Exposure Profiles and Subjective Measures of e-Vapor Products in Adult Smokers Relative to Conventional Cigarettes.



# Significant Differences in BOE and BOPH Between E-vapor Users and Cigarette Smokers<sup>1</sup>

Studies in Adult Human Subjects



<sup>1</sup> Data shared at Society for Research on Nicotine and Tobacco 2018 Annual Meeting. Oliveri et al., Cross-Sectional Study Comparing Biomarkers of Exposure to Select Harmful and Potentially Harmful Constituents and Biomarkers of Inflammation and Oxidative Stress Between Adult E-vapor Users and Conventional Cigarette Smokers.





# Clinical Studies Support MarkTen® Users Have Lower Levels of Biomarkers of Exposure and Potential Harm

Studies in Adult  
Human Subjects

## Key Takeaways:

1 Pharmacokinetics/  
Pharmacodynamics

MarkTen® portfolio offers a range of nicotine deliveries

2 Reduced Exposure 3-months

Reduced exposure and risk biomarker studies for MarkTen® are in progress

3 Reduced Risk 6-months

4 Cross-sectional category study

Significant difference in biomarkers of exposure and potential harm in exclusive users of e-vapor products compared to cigarette smokers



# ALCS Framework for Reduced Harm Tobacco Products



# Consumer Perception and Behavioral Assessment

Perception  
and Behavior  
Assessment

1 Perception and behavioral intentions

Risk perceptions and likelihood of use

2 Actual use studies

Use patterns, likelihood of switching

3 In market study

Market data on use behavior, likelihood of initiation and quitting

4 Product instruction comprehension

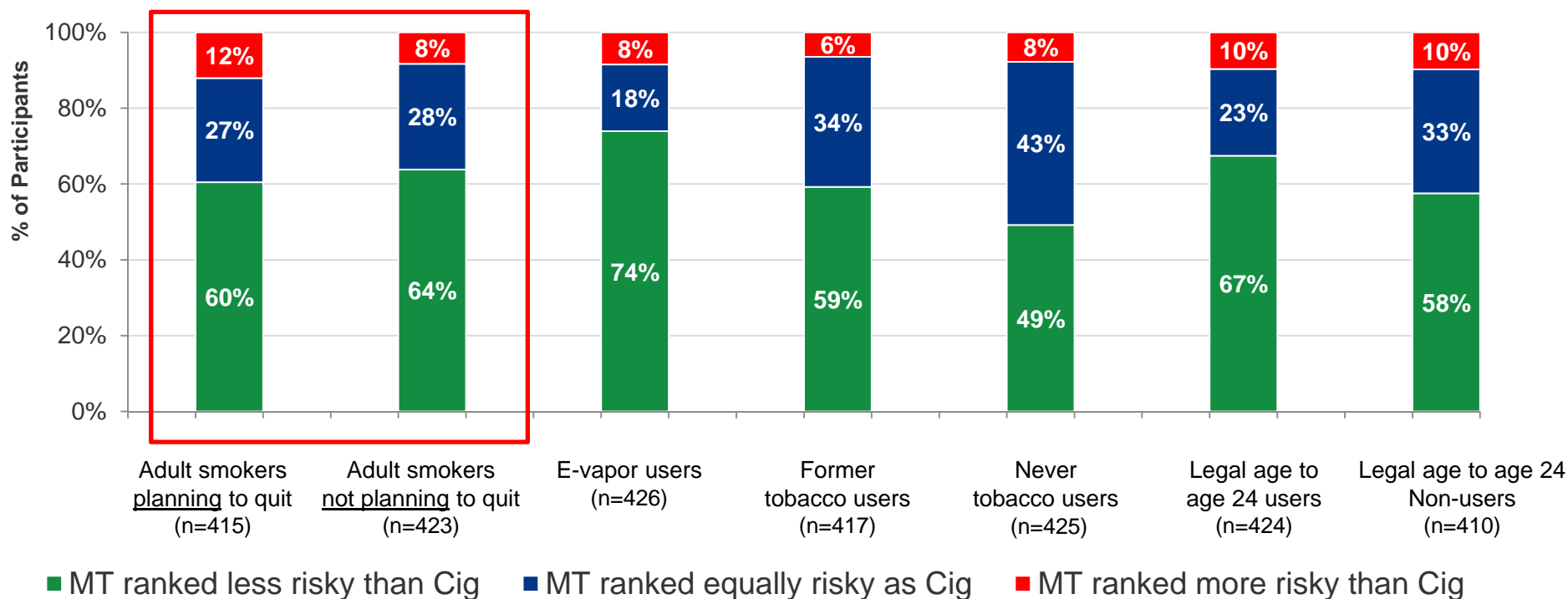
Ability to comprehend the instructions and assembly of the product



# Risk Perceptions of MarkTen<sup>®</sup> E-vapor Products Compared to Cigarettes

Perception  
and Behavior  
Assessment

Risk perception of MarkTen<sup>®</sup> relative to smoking cigarettes:  
Based on participant exposure to MarkTen<sup>®</sup> promotional materials



Source: Perceptions and Behavioral Intentions Study for Products Currently Marketed as MarkTen<sup>®</sup> E-vapor (ALCS-CMI-16-13-EV)



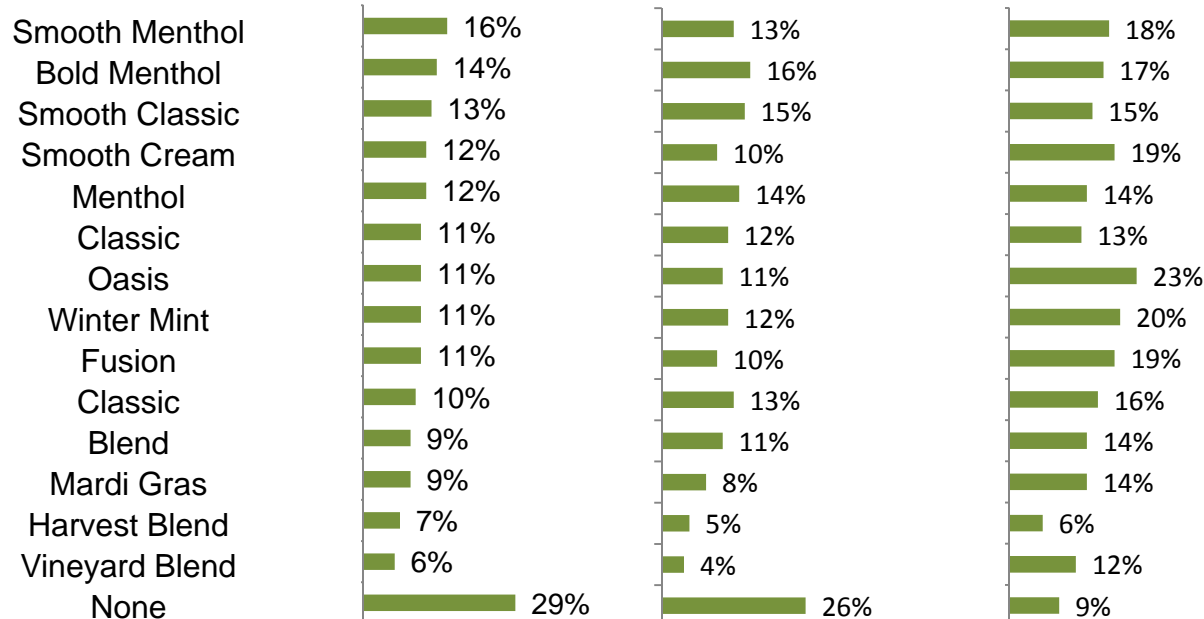
# Flavor Portfolio Maximizes Appeal of MarkTen® Products Among Adult Smokers and Vapers

Which of the following products are most appealing to you?  
(select up to 3)

Adult smokers  
planning to quit  
(N = 415)

Adult smokers NOT  
planning to quit  
(N = 423)

E-vapor users  
(N = 426)



No statistical significance testing  
Not all participants rated a product as appealing

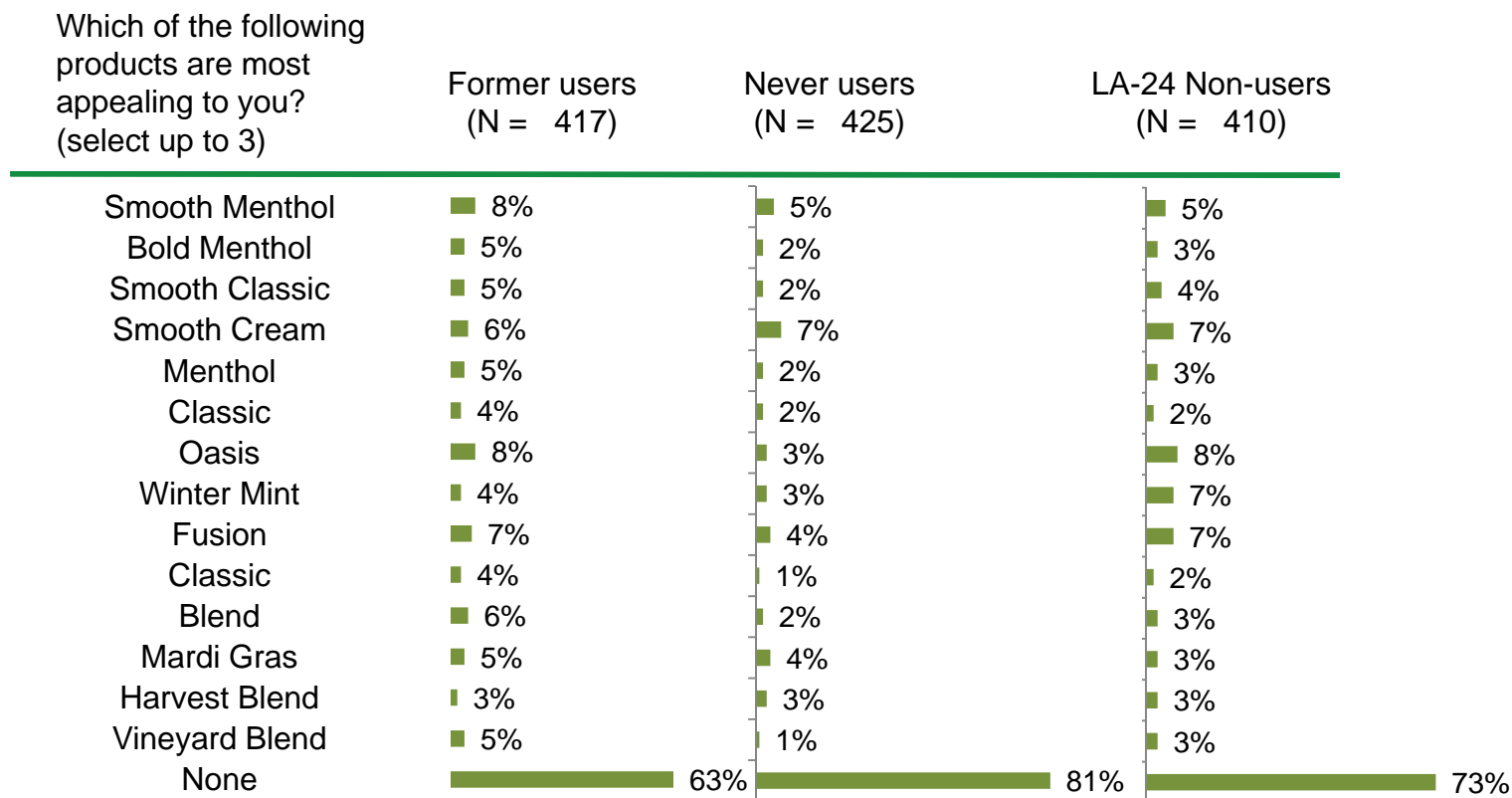
Source: Perceptions and Behavioral Intentions Study for Products Currently Marketed as MarkTen® E-vapor (ALCS-CMI-16-13-EV)





# Adult Non-tobacco Users Do Not Find MarkTen® Flavors Appealing

Perception  
and Behavior  
Assessment



No statistical significance testing  
Not all participants rated a product as appealing

Source: Perceptions and Behavioral Intentions Study for Products Currently Marketed as MarkTen® E-vapor (ALCS-CMI-16-13-EV)



# Flavor Varieties Play an Important Role in Switching

Perception  
and Behavior  
Assessment

Proportion of participants using one or more flavor varieties by cigarette consumption at Week 6

# Flavor varieties used	Total Sample n=526	Switched (0 CPD*) n=208	Decreased CPD n=257	No Change in CPD n=61
1	1.8	0.5	2.7	0
2	7.1	4.8	7	14.8
3	11.2	10.1	10.9	9.8
4	19.3	18.8	19.1	18.0
5	13.0	10.6	16.3	8.2
6	12.9	14.9	10.9	19.7
7 or more	34.7	40.4	33.1	29.5

\*CPD: Cigarettes per day



Altria

Source: A Longitudinal Study to Assess the Actual Use Of E-Vapor Products Currently Marketed as MarkTen®: MarkTen® Actual Use Study (M10-AUS)

# Every Day MarkTen<sup>®</sup> Users are More Likely to be Exclusive Users<sup>1</sup>

Perception  
and Behavior  
Assessment

	Current Users	Every day	Some days
E-cigarettes only	25%	42%	12%
E-cigarettes + 1 other tobacco product	45%	36%	52%
E-cigarettes + 2 or more other tobacco products	31%	22%	37%

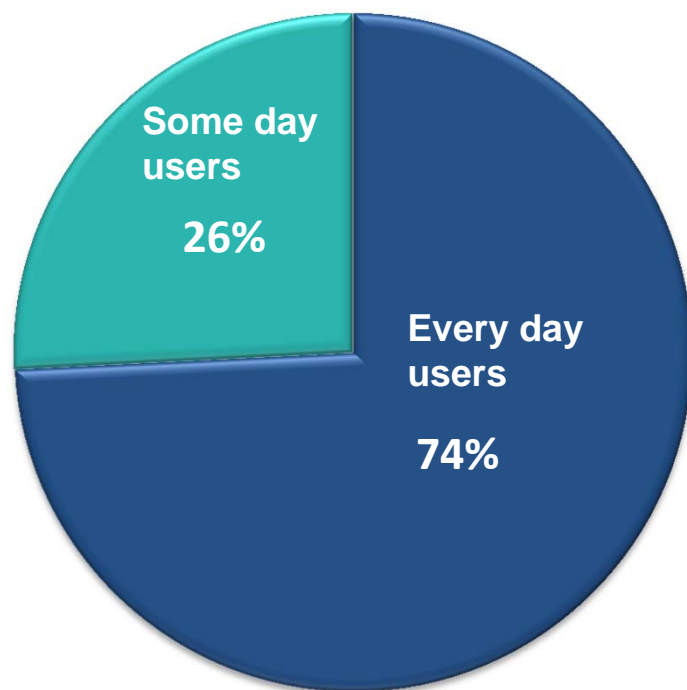


<sup>1</sup> Data shared at Society for Research on Nicotine and Tobacco 2018 Annual Meeting. Largo et al., USE PATTERNS ASSOCIATED WITH SWITCHING AND DUAL USE AMONG CURRENT CONSUMERS OF MARKTEN<sup>®</sup>XL E-VAPOR PRODUCTS

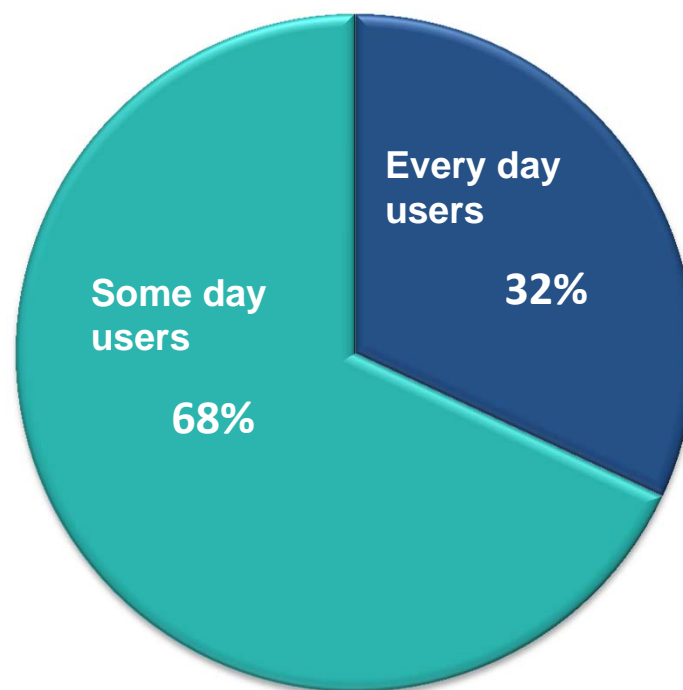
# Larger Proportion of Switchers Report Every Day MarkTen<sup>®</sup> Use<sup>1</sup>

Perception  
and Behavior  
Assessment

**Switchers**  
(n=349)



**Dual Users**  
(n=1,465)



<sup>1</sup> Data shared at Society for Research on Nicotine and Tobacco 2018 Annual Meeting. Largo et al., USE PATTERNS ASSOCIATED WITH SWITCHING AND DUAL USE AMONG CURRENT CONSUMERS OF MARKTEN<sup>®</sup>XL E-VAPOR PRODUCTS



# Beyond “satisfying nicotine cravings” Reasons for MarkTen® Use Vary by Users<sup>1</sup>

Perception  
and Behavior  
Assessment

Reasons	Switchers	Dual Users
	(n=349)	(n=1,465)
To satisfy my nicotine cravings	81%	71%
To help prevent relapse	63%	15%
To not smell like smoke/not bother other people with smoke	60%	43%
It might be less harmful than cigarettes/other tobacco products	58%	29%
Enjoy the taste	53%	45%
Has a flavor I like	46%	39%
To help cut back or quit smoking/using other tobacco products	41%	65%
It might be less harmful for other people around me	40%	30%
More affordable than cigarettes/other tobacco products	37%	25%
To use in places where I cannot/shouldn't smoke	30%	61%
So I would not have to quit using tobacco products altogether	26%	16%
Advertising or promotion (e.g., magazine ad, sign in store, coupon)	23%	34%
Interested in using this type/brand of e-cigarette	20%	24%
Curiosity	9%	16%
All other reasons	3%	2%
Don't know	1%	1%

<sup>1</sup> Data shared at Society for Research on Nicotine and Tobacco 2018 Annual Meeting. Largo et al., USE PATTERNS ASSOCIATED WITH SWITCHING AND DUAL USE AMONG CURRENT CONSUMERS OF MARKTEN®XL E-VAPOR PRODUCTS



# Consumer Perception and Behavioral Assessment

Perception  
and Behavior  
Assessment

## Key Takeaways:

### 1 Perception and behavioral intentions

Sizable portion of AS perceive MarkTen® as equally or more harmful than cigarettes

MarkTen® flavor portfolio appeals primarily to current tobacco users

### 2 Actual use studies

Flavor varieties are necessary to maximize switching

### 3 In market study

In-market data indicate every day use is associated with exclusive use of e-vapor

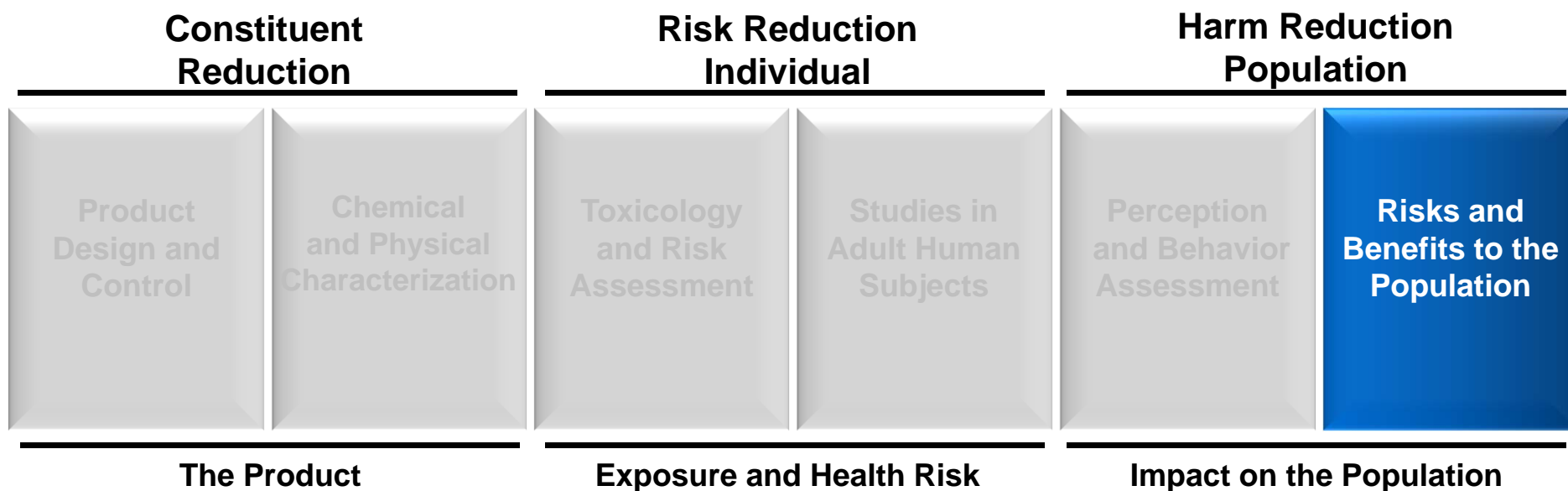
### 4 Product instruction comprehension

Product instructions are easily understood





# ALCS Framework for Reduced Harm Tobacco Products



# Population Assessment<sup>1</sup>

Risks and  
Benefits to the  
Population

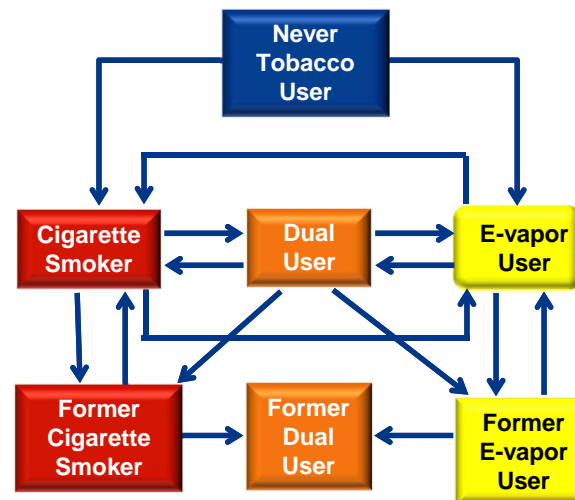
## 1 Population Modeling

Projection of likely impact on the population

### Base Case



### Modified Case



Modified Case – Base Case = Estimated change as a result of Introduction of E-vapor Product

<sup>1</sup> Data shared at Society for Research on Nicotine and Tobacco 2018 Annual Meeting. Muhammad-Kah et al., Estimating the Potential Population Health Impact of Authorizing the Marketing of E-cigarettes in the US.

# Population Assessment

Risks and  
Benefits to the  
Population

## 2 Post-Market Surveillance

Passive and active monitoring the impact of the introduction of the new product into the market

	Active Surveillance				Passive Surveillance		
Consumer Health		■	■	■	■		
Consumer Behavior	■	■	■	■	■		
Consumer Perception	■	■	■	■	■		
Adverse Events			■		■	■	■
	In-market cross-sectional surveys	Prospective observational studies	Literature reviews	National surveys and studies (e.g. PATH)	Internet forum monitoring (pending validation)	Call center AEs monitoring	Poison center registration



# Overall Conclusions

- E-vapor products present an opportunity to reduce the harm from cigarette smoking
- We have a rigorous process to develop and evaluate our e-vapor products to demonstrate harm reduction opportunity
- To advance harm reduction
  - Generate sound science
  - Truthful and accurate communications about relative risk
  - Reframe debate about nicotine
  - Transparent and reasonable product pathways that foster innovation

