

Tobacco Harm Reduction

E-Vapor Products

Maria Gogova, M.D., Ph.D.
April 24, 2018

Next Generation Nicotine Delivery Conference



Altria

Altria Client Services

Cigarette Smoking: A Significant Public Health Problem

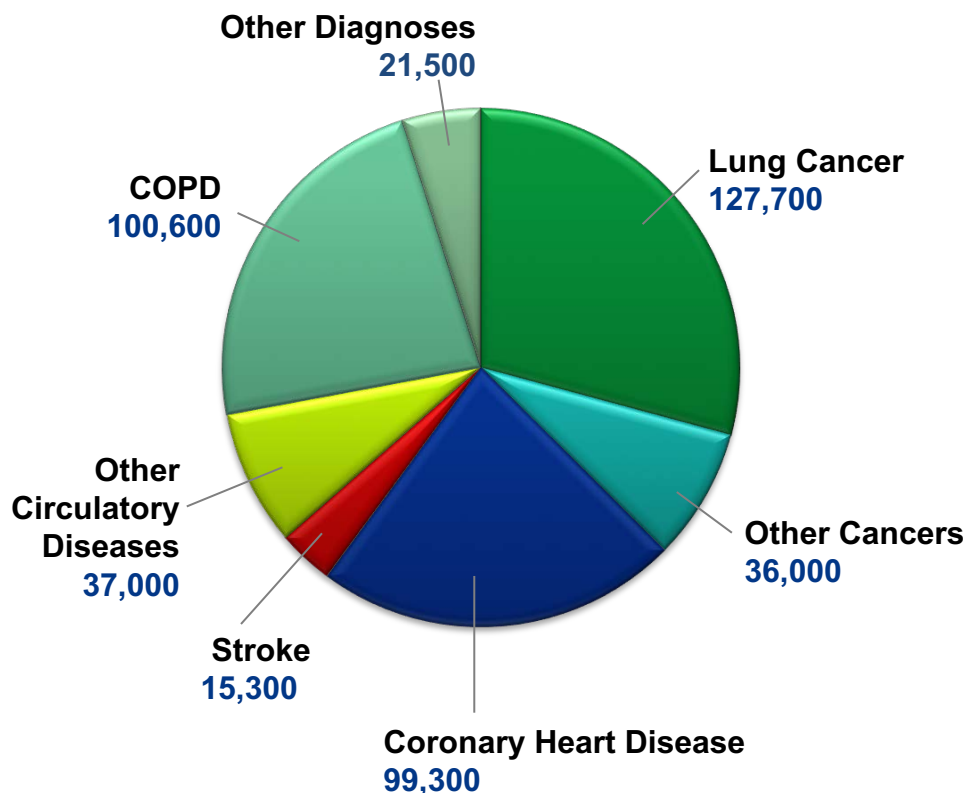
Cigarette smoking causes about **one of every five deaths** annually in the U.S

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

Diseases Caused by Cigarette Smoking

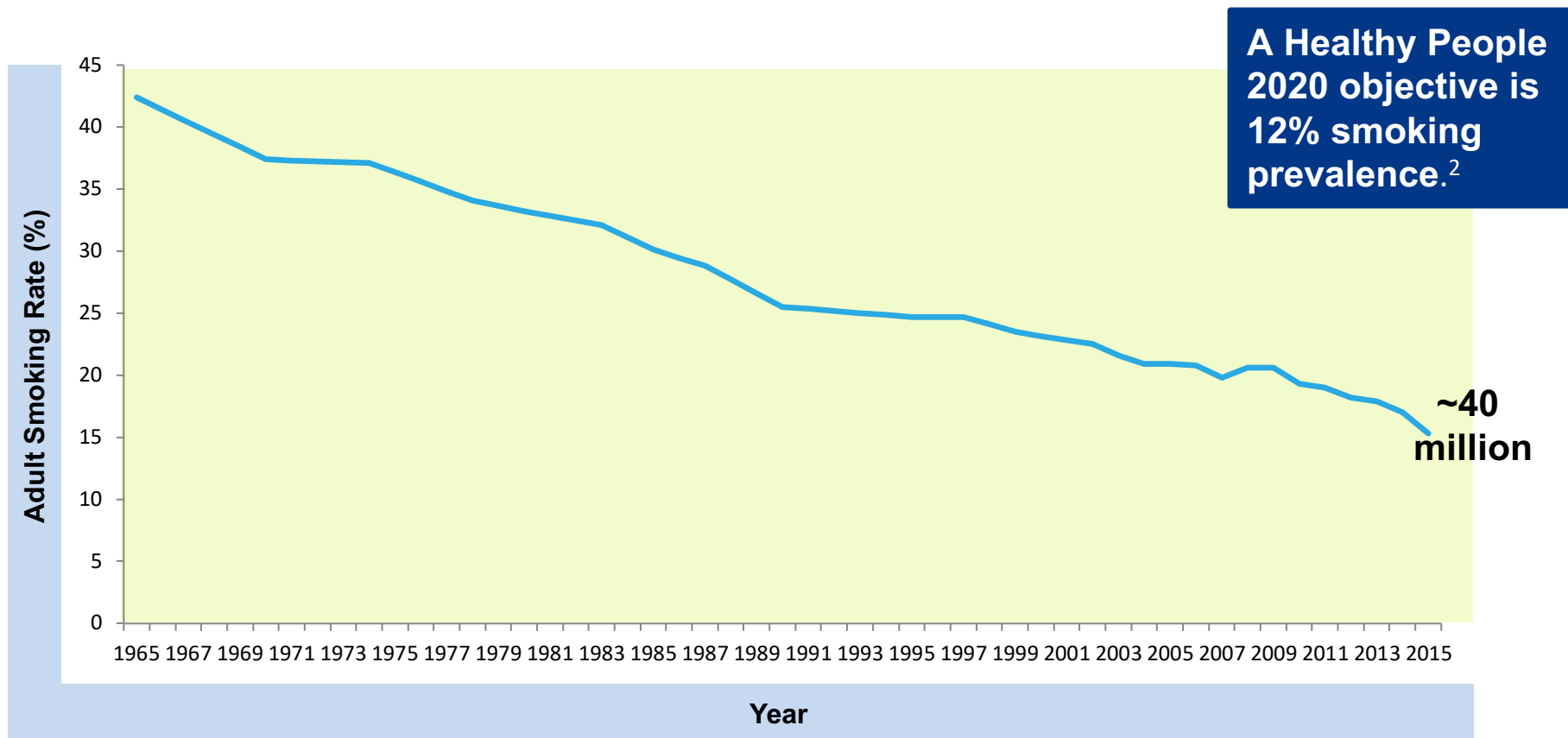


- The most hazardous form of tobacco consumption is burning tobacco and inhaling the smoke.
- There is overwhelming evidence that cigarette smoking is addictive and causes serious diseases such as:
 - Lung cancer
 - COPD
 - Cardiovascular disease

Attributable Mortality Among Cigarette Smokers

http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm

Cigarette Smoking Trends Among U.S. Adults 1965 – 2015¹



¹ http://www.cdc.gov/tobacco/data_statistics/tables/trends/cig_smoking/index.htm

² <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
HARMFUL**



Altria

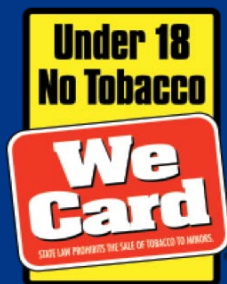
July 28, 2017: Protecting American Families: Comprehensive Approach to Nicotine and Tobacco
<https://www.fda.gov/NewsEvents/Speeches/ucm569024.htm>

Altria Supports Harm Reduction in a Variety of Ways

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



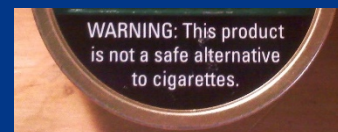
**Help Reduce
Underage
Tobacco Use**



**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

Tobacco Harm Reduction Product Platforms

E-Vapor

MARKTEN®



Oral Tobacco/ Nicotine Products



Heated Tobacco Products

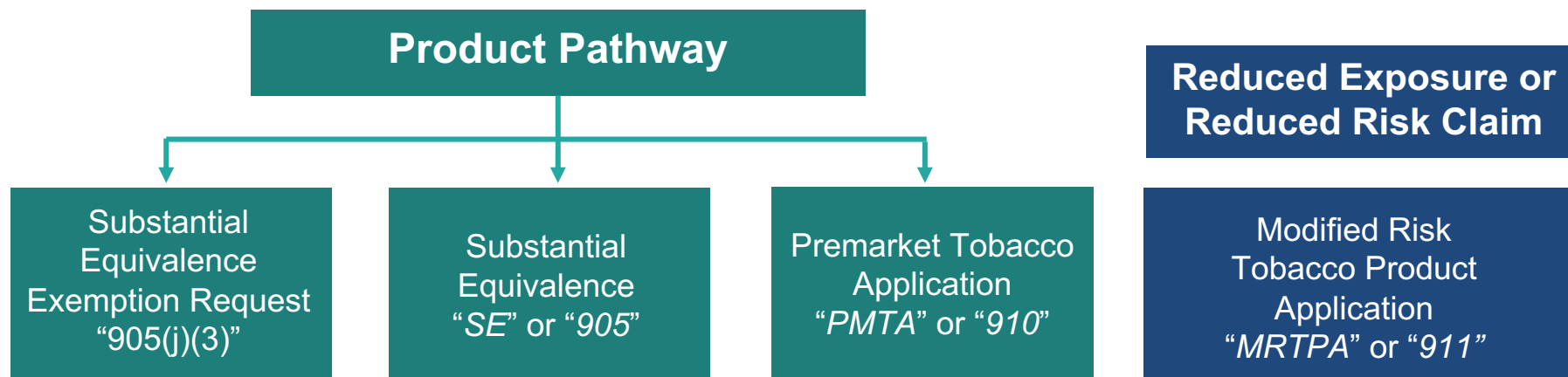
IQOS®
THIS CHANGES EVERYTHING



Diverse E-vapor Product Portfolio



FDA Market Pathways



MarkTen® E-Vapor Products Portfolio



Altria

ALCS Framework for Reduced Harm Tobacco Products

Constituent Reduction

Product Design and Control

Chemical and Physical Characterization

The Product

Risk Reduction Individual

Toxicology and Risk Assessment

Studies in Adult Human Subjects

Exposure and Health Risk

Harm Reduction Population

Perception and Behavior Assessment

Risks and Benefits to the Population

Impact on the Population

ALCS Framework for Reduced Harm Tobacco Products

Constituent Reduction

Product Design and Control

Chemical and Physical Characterization

The Product

Risk Reduction Individual

Toxicology and Risk Assessment

Studies in Adult Human Subjects

Exposure and Health Risk

Harm Reduction Population

Perception and Behavior Assessment

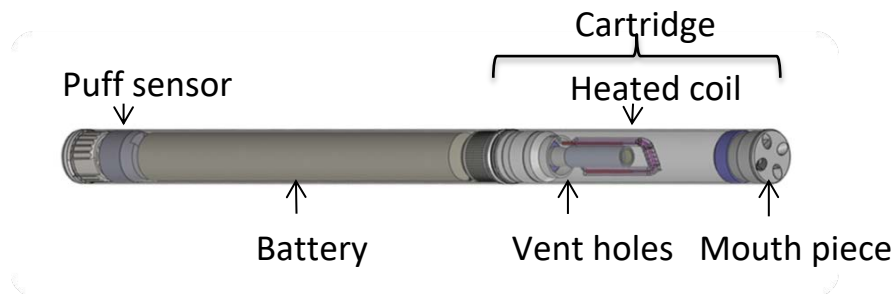
Risks and Benefits to the Population

Impact on the Population

MarkTen[®] Product was Designed to Eliminate or Significantly Reduce HPHC¹ 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

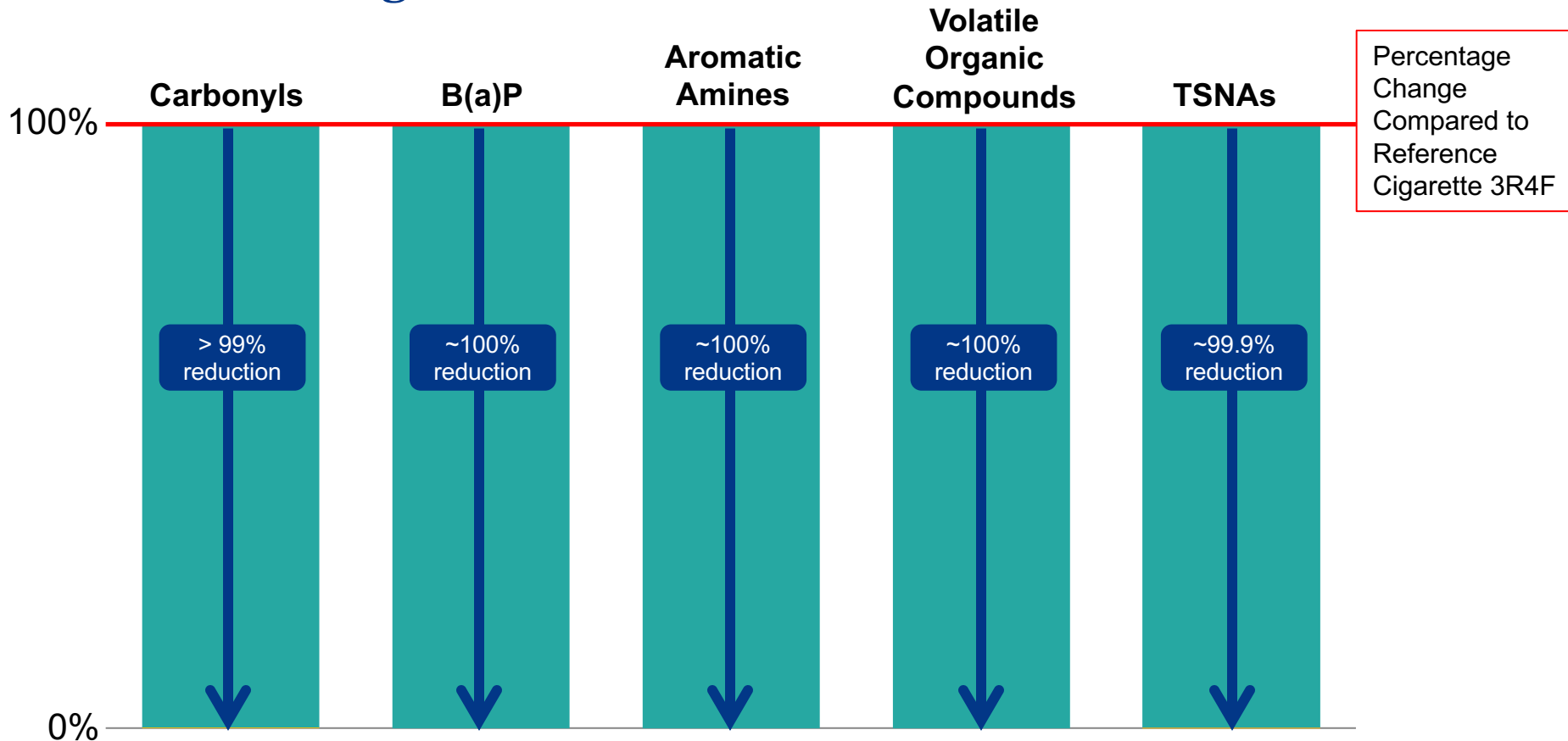
Elimination or reduced formation

- Selected HPHC
- Other targeted constituents (e.g. metals)

¹ HPHC = Harmful or Potentially Harmful Constituents

Harmful and Potentially Harmful Constituents in MarkTen[®] Aerosol Are Substantially Lower Than Reference Cigarettes

Chemical
and Physical
Characterization



ALCS Internal Report LIQUID 16241 – MarkTen[®] 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

Constituent Reduction

Product Design and Control

Chemical and Physical Characterization

The Product

Risk Reduction Individual

Toxicology and Risk Assessment

Studies in Adult Human Subjects

Exposure and Health Risk

Harm Reduction Population

Perception and Behavior Assessment

Risks and Benefits to the Population

Impact on the Population

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

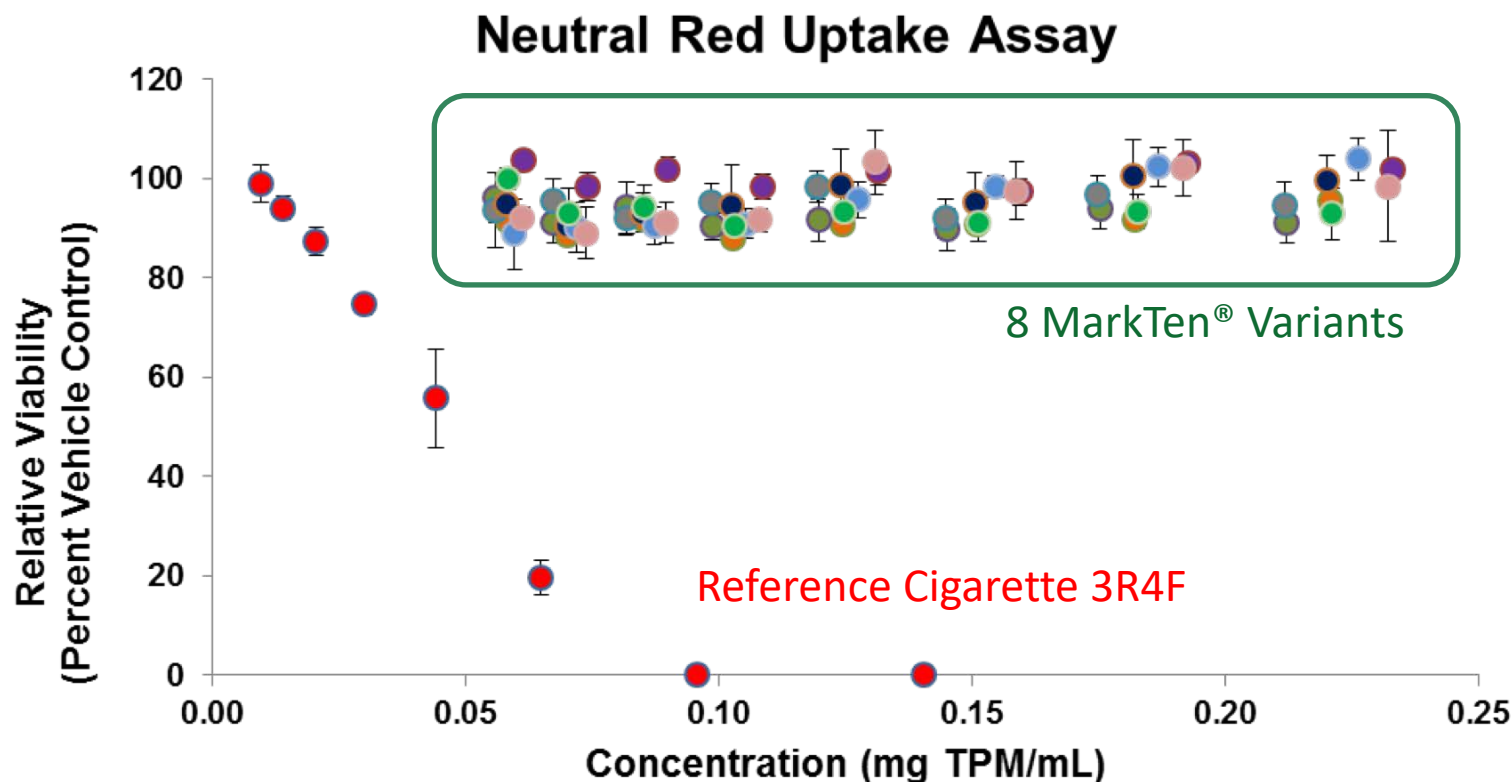
4 E-liquid and aerosol condensate

In-vitro toxicology studies

- OECD guidelines
- Cytotoxicity and genotoxicity

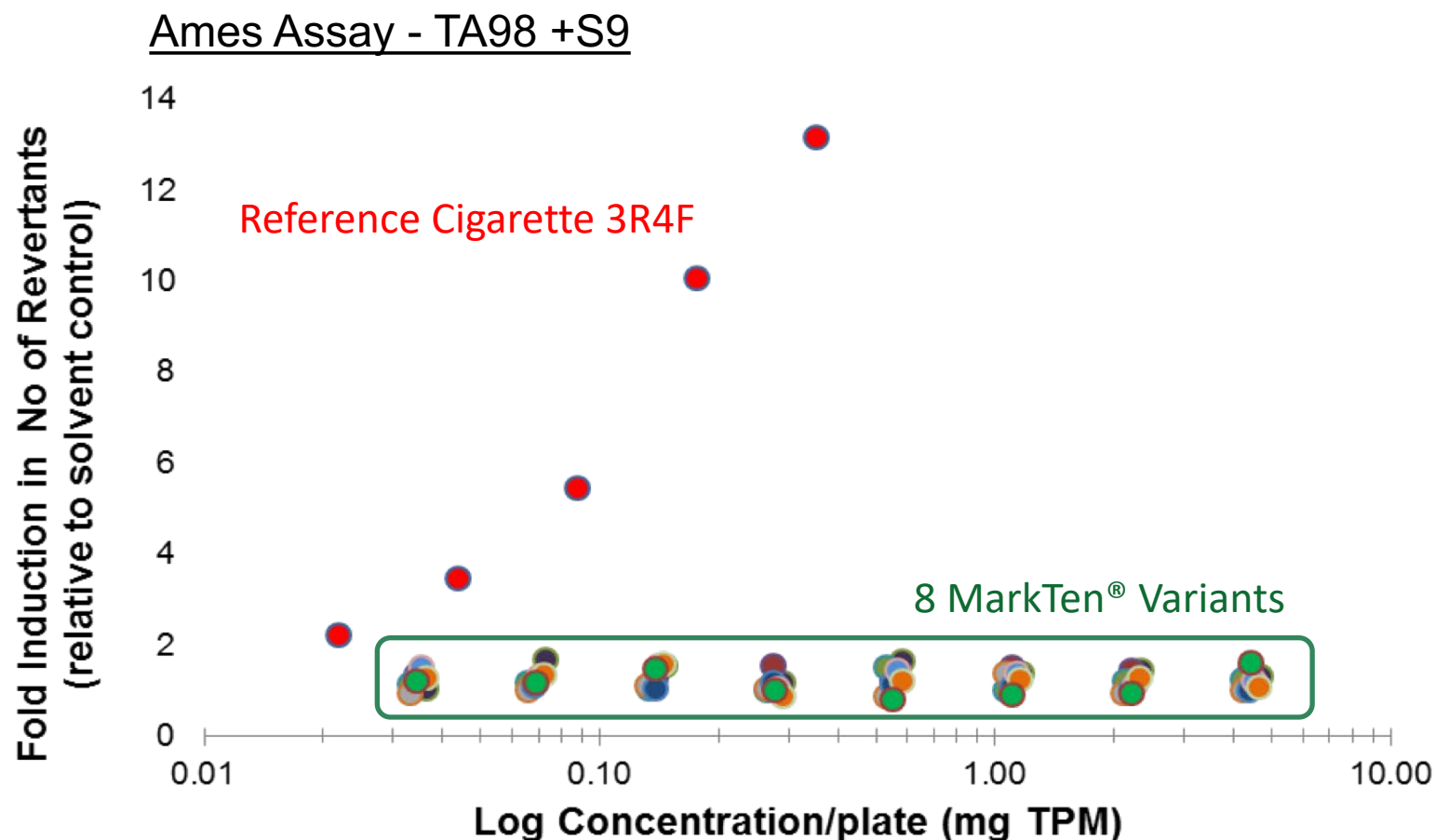
No Cytotoxicity Observed from MarkTen[®] Aerosol Condensates in Neutral Red Uptake Assays¹

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)

No Mutagenicity Response Observed from MarkTen[®] Aerosol Condensates in Ames Test¹



¹ 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

Constituent Reduction

Product Design and Control

Chemical and Physical Characterization

The Product

Risk Reduction Individual

Toxicology and Risk Assessment

Studies in Adult Human Subjects

Exposure and Health Risk

Harm Reduction Population

Perception and Behavior Assessment

Risks and Benefits to the Population

Impact on the Population

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

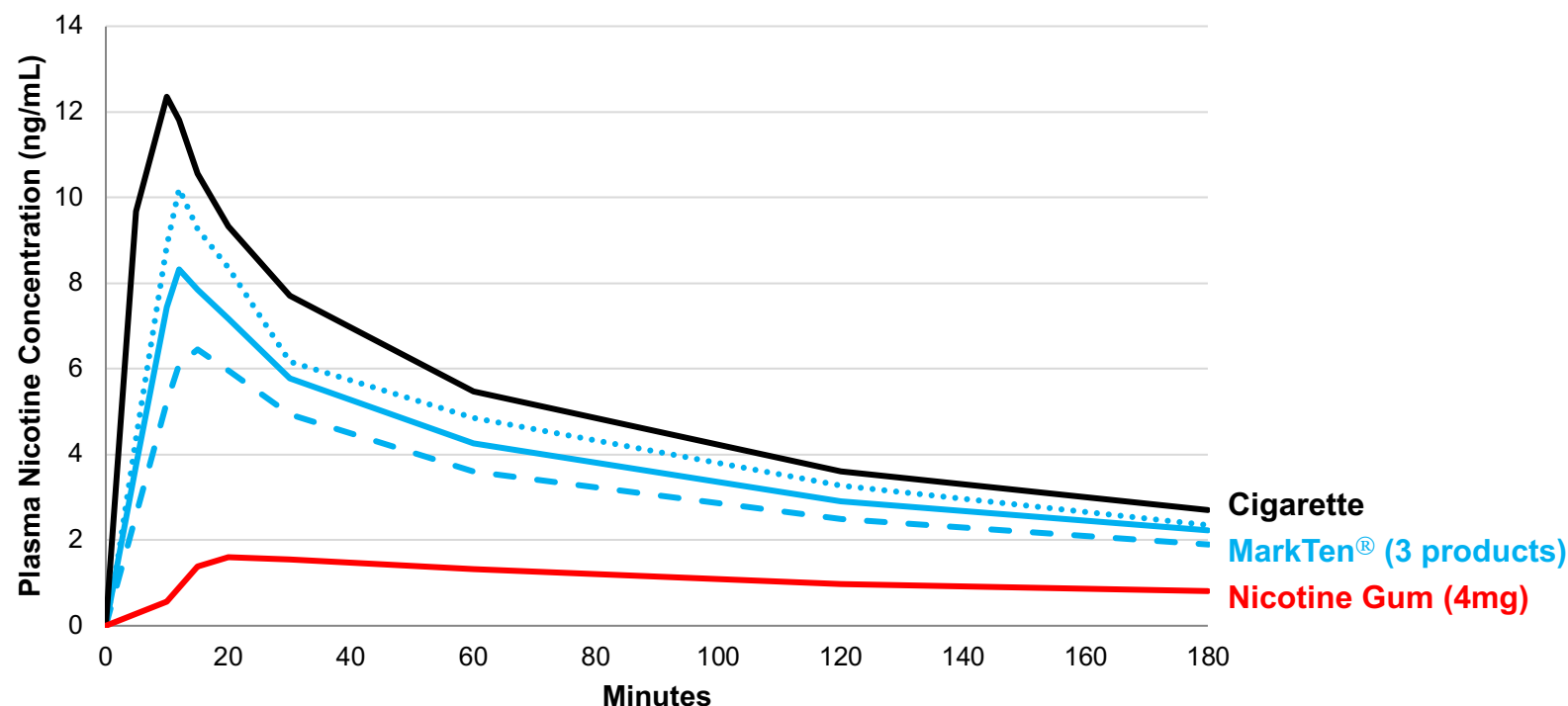
Impact on non-users

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.



MarkTen[®] Nicotine Pharmacokinetic Studies Demonstrate a Range of Nicotine Deliveries¹

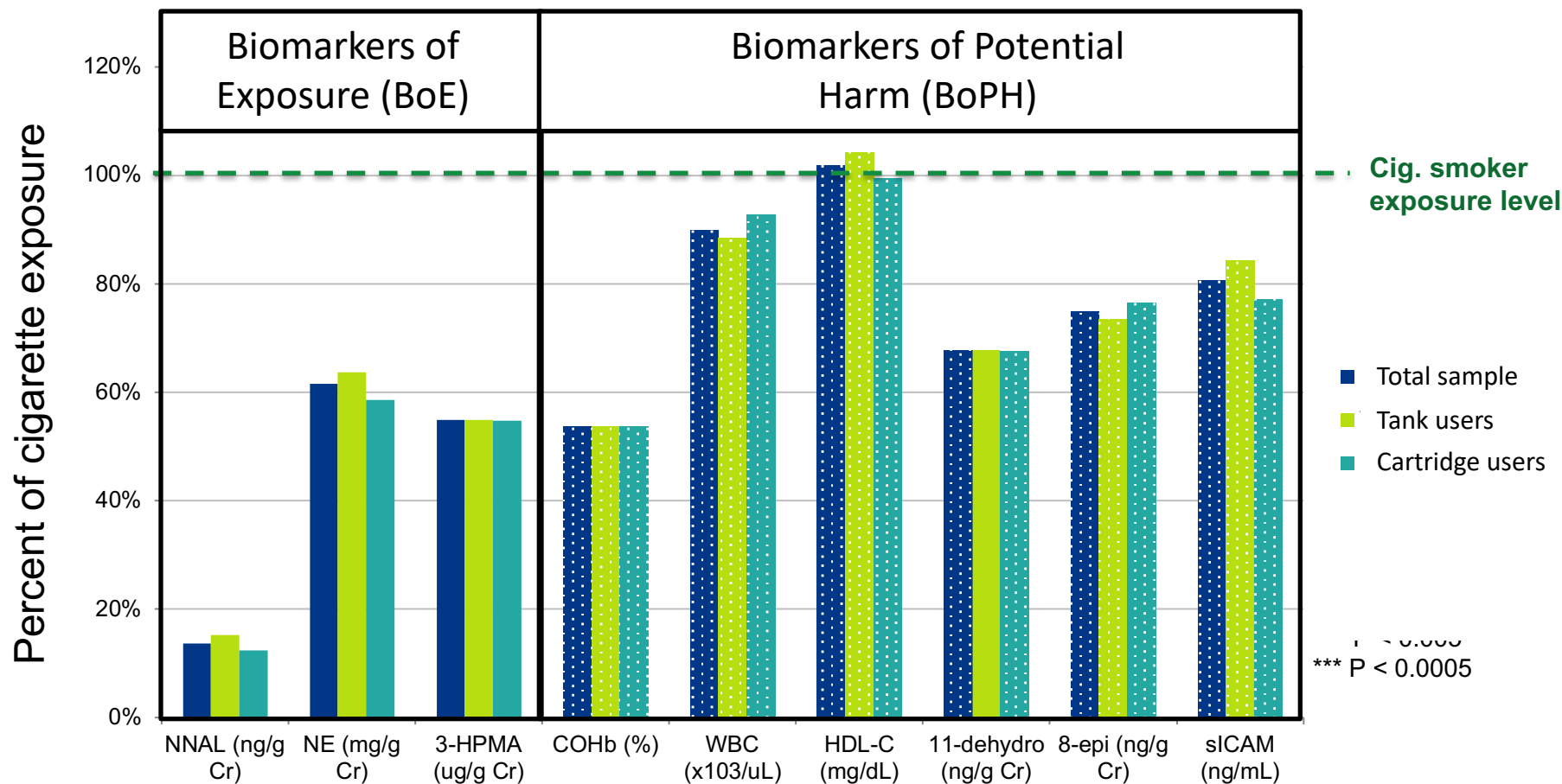
Studies in Adult Human Subjects



¹ 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 Smokers¹

Studies in Adult Human Subjects



¹ 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

Constituent Reduction

Product Design and Control

Chemical and Physical Characterization

The Product

Risk Reduction Individual

Toxicology and Risk Assessment

Studies in Adult Human Subjects

Exposure and Health Risk

Harm Reduction Population

Perception and Behavior Assessment

Risks and Benefits to the Population

Impact on the Population

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

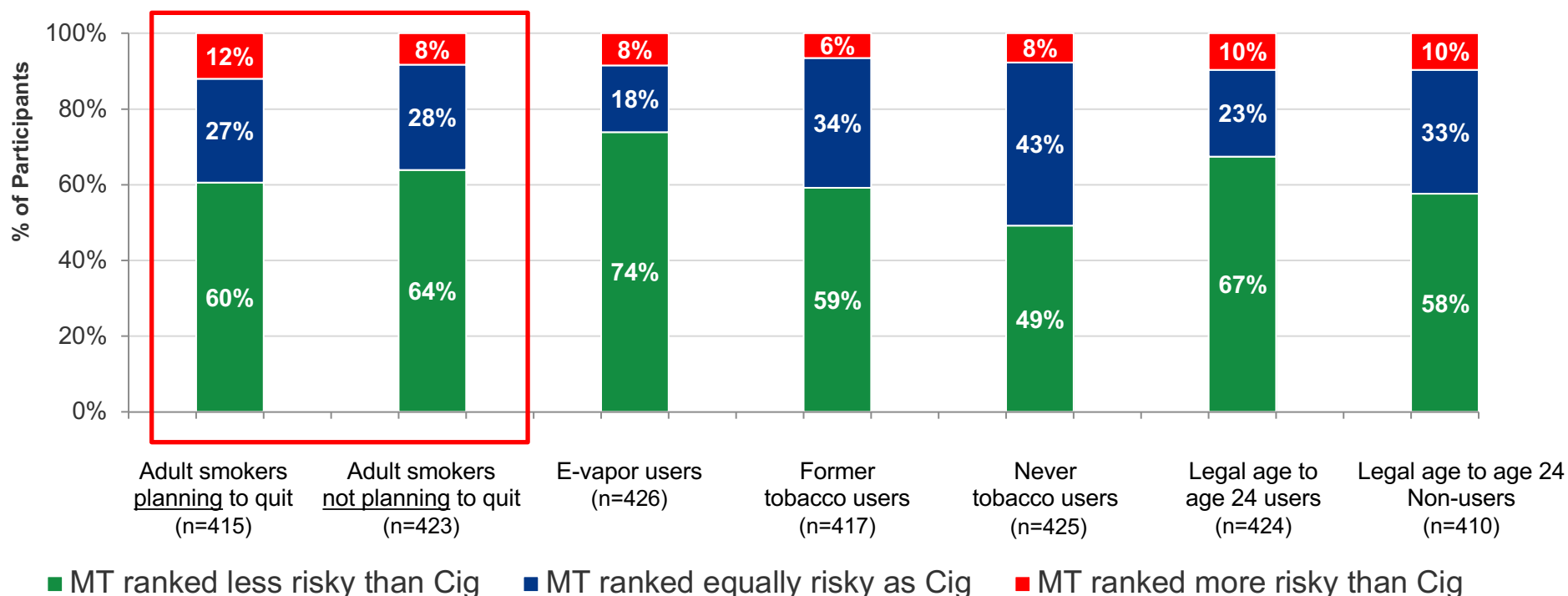
4 Product instruction
comprehension

Ability to comprehend the instructions and assembly of the product

Risk Perceptions of MarkTen® E-vapor Products Compared to Cigarettes

Perception
and Behavior
Assessment

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



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



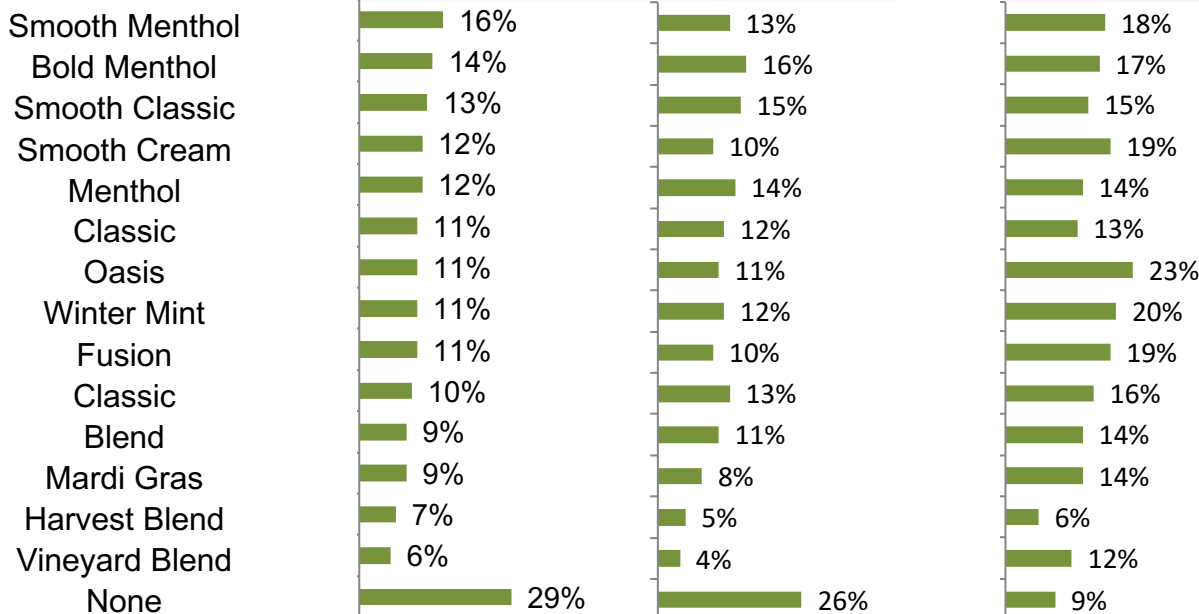
Flavor Portfolio Maximizes Appeal of MarkTen® Products Among Adult Smokers and Vapers

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)



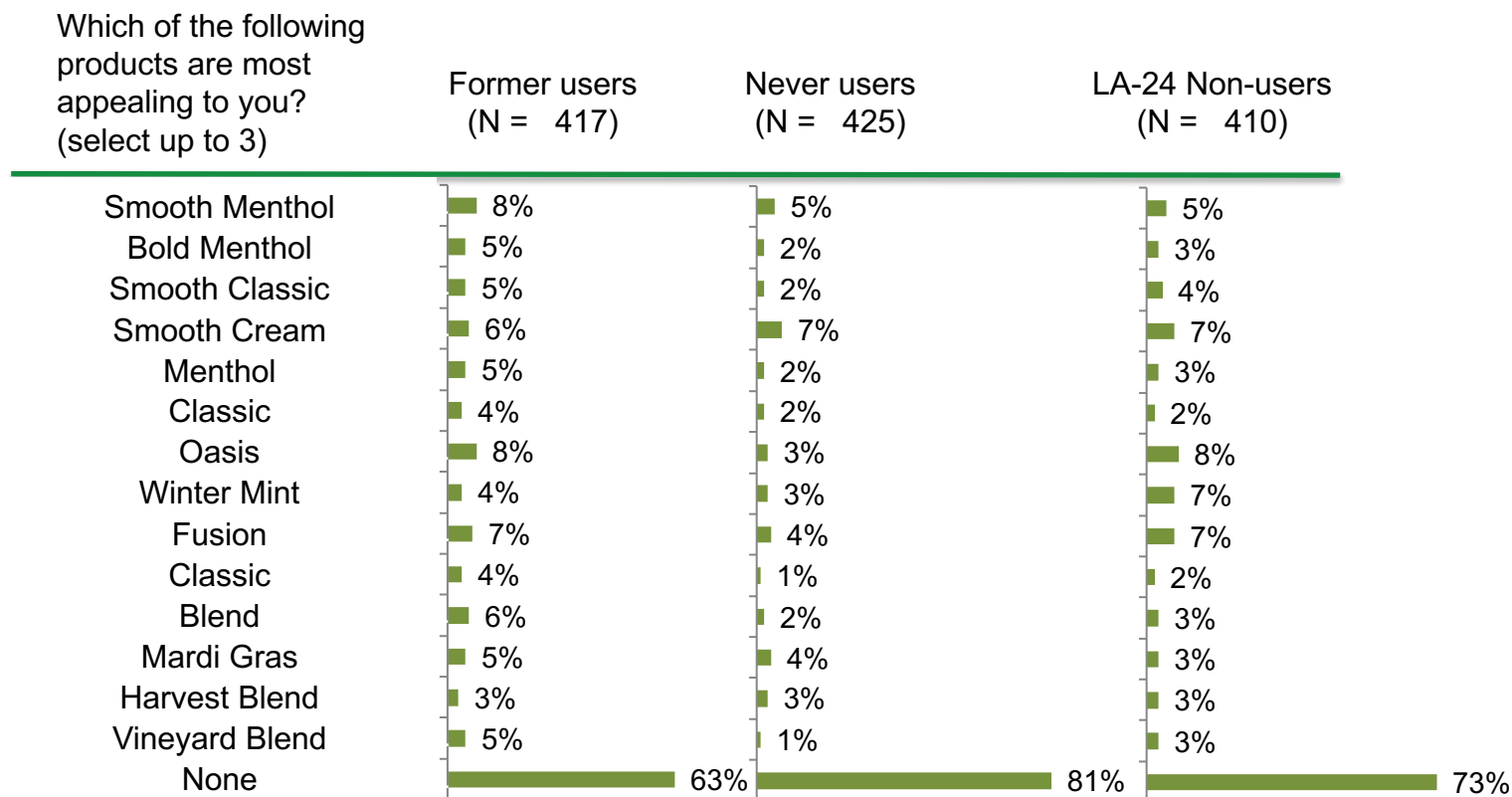
No statistical significance testing

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[®] Users are More Likely to be Exclusive Users¹

Perception
and Behavior
Assessment

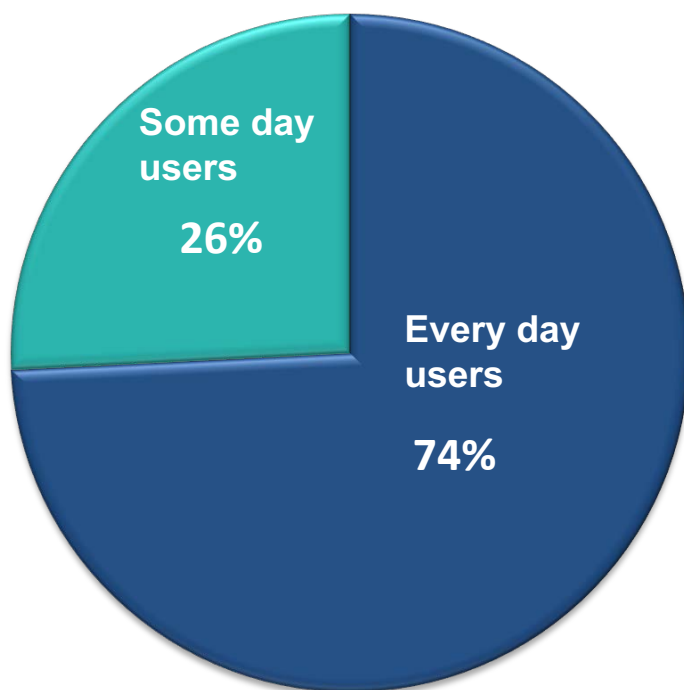
	Current Users	Every day	Some days
E-cigarettes only	25%	42%	12%
E-cigarettes + 1 other tobacco product	45%	36%	52%
E-cigarettes + 2 or more other tobacco products	31%	22%	37%

¹ 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

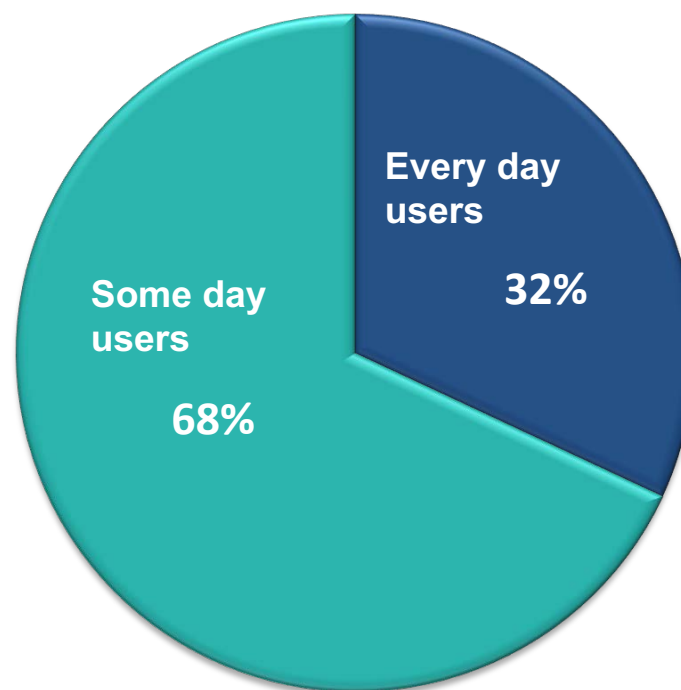
Larger Proportion of Switchers Report Every Day MarkTen® Use¹

Perception
and Behavior
Assessment

Switchers
(n=349)



Dual Users
(n=1,465)



¹ 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

Beyond “satisfying nicotine cravings” Reasons for MarkTen® Use Vary by Users¹

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%

¹ 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

Constituent Reduction

Product Design and Control

Chemical and Physical Characterization

The Product

Risk Reduction Individual

Toxicology and Risk Assessment

Studies in Adult Human Subjects

Exposure and Health Risk

Harm Reduction Population

Perception and Behavior Assessment

Risks and Benefits to the Population

Impact on the Population

Population Assessment¹

Risks and
Benefits to the
Population

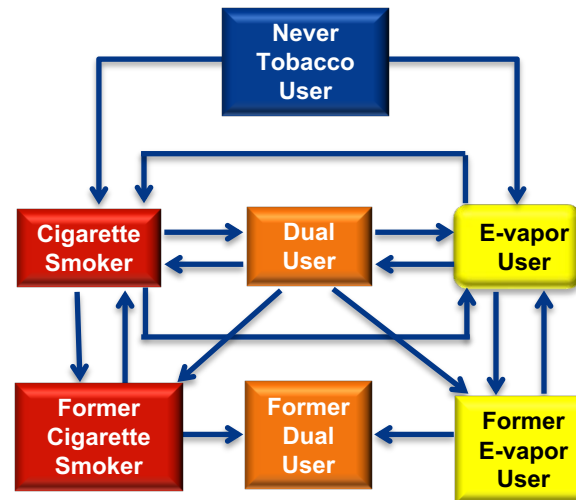
1 Population Modeling

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

¹ 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
 - Reframe debate about nicotine
 - Truthful and accurate communications about relative risk
 - Transparent and reasonable product pathways that foster innovation

