Tobacco Harm Reduction

E-Vapor Products

Michael Fisher, Ph.D.
June 8, 2018

1st Scientific Summit on Tobacco Harm Reduction
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_control_mortality/index.html#age
Cigarette Smoking Trends Among U.S. Adults 1965 – 2015

A Healthy People 2020 objective is 12% smoking prevalence.

~40 million

1 http://www.cdc.gov/tobacco/data_statistics/tables/trends/cig_smoking/index.htm
2 https://www.healthypeople.gov/
“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

July 28, 2017: Protecting American Families: Comprehensive Approach to Nicotine and Tobacco
https://www.fda.gov/NewsEvents/Speeches/ucm569024.htm
Our long-term goal at Altria is to achieve a leadership position in innovative and reduced risk tobacco products.
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

~40 MM
Adult Cigarette Smokers

~5 MM
Adult Smokeless Consumers

~10 MM
Adult E-Vapor Consumers

*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

Product Pathway

- Substantial Equivalence Exemption Request “905(j)(3)”
- Substantial Equivalence “SE” or “905”
- Premarket Tobacco Application “PMTA” or “910”

Reduced Exposure or Reduced Risk Claim

- Modified Risk Tobacco Product Application “MRTPA” or “911”
ALCS Framework for Reduced Harm Tobacco Products

Constituent Reduction
- Product Design and Control
- Chemical and Physical Characterization

Risk Reduction Individual
- Toxicology and Risk Assessment
- Studies in Adult Human Subjects

Harm Reduction Population
- Perception and Behavior Assessment
- Risks and Benefits to the Population

The Product
Exposure and Health Risk
Impact on the Population
## ALCS Framework for Reduced Harm Tobacco Products

<table>
<thead>
<tr>
<th>Constituent Reduction</th>
<th>Risk Reduction Individual</th>
<th>Harm Reduction Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Design and Control</td>
<td>Toxicology and Risk Assessment</td>
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<td>Chemical and Physical Characterization</td>
<td>Studies in Adult Human Subjects</td>
<td>Risks and Benefits to the Population</td>
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</table>

- **The Product**
- **Exposure and Health Risk**
- **Impact on the Population**
MarkTen® Product was Designed to Eliminate or Significantly Reduce HPHC\(^1\) Generation

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

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

- **Carbonyls**: > 99% reduction
- **B(a)P**: ~100% reduction
- **Aromatic Amines**: ~100% reduction
- **Volatile Organic Compounds**: ~100% reduction
- **TSNAs**: ~99.9% reduction

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

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The Product

Exposure and Health Risk

Impact on the Population
Reduced Risk Assessment: Pre-Clinical Studies

1. Ingredients risk assessment
2. Carrier assessment
3. Flavor assessment
4. E-liquid and aerosol condensate

Toxicological literature review
Flavors and carriers are:
- Generally recognized as safe (GRAS) for use in foods
- Food or pharmaceutical grade

90 day in-vivo studies

In-vitro toxicology studies
- OECD guidelines
- Cytotoxicity and genotoxicity
No Cytotoxicity Observed from MarkTen® Aerosol Condensates in Neutral Red Uptake Assays

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

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.
No Mutagenicity Response Observed from MarkTen® Aerosol Condensates in Ames Test

Ames Assay - TA98 +S9

Fold Induction in No of Revertants (relative to solvent control)

Reference Cigarette 3R4F

8 MarkTen® Variants

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

Key Takeaways:

1. Ingredients risk assessment
   No treatment related effects
   - Survival
   - Body weight
   - Clinical observations & chemistry parameters
   - Histopathology

2. Carrier assessment
3. Flavor assessment

4. E-liquid and aerosol condensate
   No evidence of mutagenicity or cytotoxicity

Altria
# ALCS Framework for Reduced Harm Tobacco Products

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## The Product

- Constituent Reduction
- Risk Reduction Individual
- Harm Reduction Population

## Exposure and Health Risk

- The Product Exposure and Health Risk Impact on the Population

## Impact on the Population

- Risks and Benefits to the Population

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

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 Deliveries

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 Smokers

<table>
<thead>
<tr>
<th>Percent of cigarette exposure</th>
<th>Biomarkers of Exposure (BoE)</th>
<th>Biomarkers of Potential Harm (BoPH)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NNAL (ng/g Cr)</td>
<td>WBC (x10³/uL)</td>
</tr>
<tr>
<td></td>
<td>NE (mg/g Cr)</td>
<td>HDL-C (mg/dL)</td>
</tr>
<tr>
<td></td>
<td>3-HPMA (ug/g Cr)</td>
<td>11-dehydro (ng/g Cr)</td>
</tr>
<tr>
<td></td>
<td>COHb (%)</td>
<td>8-epi (ng/g Cr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sICAM (ng/mL)</td>
</tr>
</tbody>
</table>

Cig. smoker exposure level

- Total sample
- Tank users
- Cartridge users

* P < 0.05
** P < 0.005
*** P < 0.0005

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

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

4. Cross-sectional category study
ALCS Framework for Reduced Harm Tobacco Products

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The Product
Exposure and Health Risk
Impact on the Population
Consumer Perception and Behavioral 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

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

- **Adult smokers planning to quit (n=415)**
  - MT ranked less risky than Cig: 60%
  - MT ranked equally risky as Cig: 27%
  - MT ranked more risky than Cig: 12%

- **Adult smokers not planning to quit (n=423)**
  - MT ranked less risky than Cig: 64%
  - MT ranked equally risky as Cig: 28%
  - MT ranked more risky than Cig: 8%

- **E-vapor users (n=426)**
  - MT ranked less risky than Cig: 74%
  - MT ranked equally risky as Cig: 18%
  - MT ranked more risky than Cig: 8%

- **Former tobacco users (n=417)**
  - MT ranked less risky than Cig: 59%
  - MT ranked equally risky as Cig: 34%
  - MT ranked more risky than Cig: 6%

- **Never tobacco users (n=425)**
  - MT ranked less risky than Cig: 49%
  - MT ranked equally risky as Cig: 43%
  - MT ranked more risky than Cig: 8%

- **Legal age to age 24 users (n=424)**
  - MT ranked less risky than Cig: 67%
  - MT ranked equally risky as Cig: 23%
  - MT ranked more risky than Cig: 10%

- **Legal age to age 24 Non-users (n=410)**
  - MT ranked less risky than Cig: 58%
  - MT ranked equally risky as Cig: 33%
  - MT ranked more risky than Cig: 10%

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

<table>
<thead>
<tr>
<th>Flavor</th>
<th>Adult smokers planning to quit (N = 415)</th>
<th>Adult smokers NOT planning to quit (N = 423)</th>
<th>E-vapor users (N = 426)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth Menthol</td>
<td>16%</td>
<td>13%</td>
<td>18%</td>
</tr>
<tr>
<td>Bold Menthol</td>
<td>14%</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Smooth Classic</td>
<td>13%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Smooth Cream</td>
<td>12%</td>
<td>10%</td>
<td>19%</td>
</tr>
<tr>
<td>Menthol</td>
<td>12%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Classic</td>
<td>11%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Oasis</td>
<td>11%</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>Winter Mint</td>
<td>11%</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>Fusion</td>
<td>11%</td>
<td>10%</td>
<td>19%</td>
</tr>
<tr>
<td>Classic</td>
<td>10%</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>Blend</td>
<td>9%</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>Mardi Gras</td>
<td>9%</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>Harvest Blend</td>
<td>7%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Vineyard Blend</td>
<td>6%</td>
<td>4%</td>
<td>12%</td>
</tr>
<tr>
<td>None</td>
<td>29%</td>
<td>26%</td>
<td>9%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Former users (N = 417)</th>
<th>Never users (N = 425)</th>
<th>LA-24 Non-users (N = 410)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth Menthol</td>
<td>8%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Bold Menthol</td>
<td>5%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Smooth Classic</td>
<td>5%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Smooth Cream</td>
<td>6%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Menthol</td>
<td>5%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Classic</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Oasis</td>
<td>8%</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Winter Mint</td>
<td>4%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Fusion</td>
<td>7%</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Classic</td>
<td>4%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Blend</td>
<td>6%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Mardi Gras</td>
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<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Harvest Blend</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Vineyard Blend</td>
<td>5%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>None</td>
<td>63%</td>
<td>81%</td>
<td>73%</td>
</tr>
</tbody>
</table>

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

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

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

*CPD: Cigarettes per day

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 Users\(^1\)

<table>
<thead>
<tr>
<th>Perception and Behavior Assessment</th>
<th>Current Users</th>
<th>Every day</th>
<th>Some days</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-cigarettes only</td>
<td>25%</td>
<td>42%</td>
<td>12%</td>
</tr>
<tr>
<td>E-cigarettes + 1 other tobacco product</td>
<td>45%</td>
<td>36%</td>
<td>52%</td>
</tr>
<tr>
<td>E-cigarettes + 2 or more other tobacco products</td>
<td>31%</td>
<td>22%</td>
<td>37%</td>
</tr>
</tbody>
</table>

\(^1\) 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® Use

Switchers (n=349)

- Some day users: 26%
- Every day users: 74%

Dual Users (n=1,465)

- Some day users: 32%
- Every day users: 68%

---

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 Users

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

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

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

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Harm Reduction Population
- Perception and Behavior Assessment

The Product
Exposure and Health Risk
Impact on the Population

Risks and Benefits to the Population
Population Assessment

1 Population Modeling

Projection of likely impact on the population

Base Case

- Never Tobacco User
  - Cigarette Smoker
  - Former Cigarette Smoker

Modified Case

- Never Tobacco User
  - Cigarette Smoker
  - Former Cigarette Smoker
  - Dual User
    - E-vapor User
  - Former Dual User
  - Former E-vapor User

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

## Population Assessment

### Post-Market Surveillance

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

<table>
<thead>
<tr>
<th>Active Surveillance</th>
<th>Passive Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumer Health</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Consumer Behavior</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Consumer Perception</td>
<td></td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Adverse Events</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In-market cross-sectional surveys</th>
<th>Prospective observational studies</th>
<th>Literature reviews</th>
<th>National surveys and studies (e.g. PATH)</th>
<th>Internet forum monitoring (pending validation)</th>
<th>Call center AEs monitoring</th>
<th>Poison center registration</th>
</tr>
</thead>
</table>
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