Industry Engagement with the Scientific Community

Willie J. McKinney, PhD, DABT
June 6, 2018
Tobacco Harm Reduction as a Common Goal?

Industry

Regulators

Academic Scientists
Science & Evidence
Barriers to Collaboration & Engagement within the Tobacco Industry

“As editors of the BMJ, Heart, Thorax and BMJ Open, we have decided that the journals will no longer consider for publication any study that is partly or wholly funded by the tobacco industry. Our new policy is consistent with those of other journals including PLoS Medicine, PLoS One, PLoS Biology, Journal of Health Psychology, journals published by the American Thoracic Society, and the BMJ's own Tobacco Control.”

Source: http://thorax.bmj.com/content/68/12/1090 on 5/9/2018

“Editor: We recognise the tobacco industry is a controversial subject for many readers. However, many chemists work in this field and we are committed to providing an accurate representation of career paths. This article aims to provide an insight into a chemist’s working life and should not be interpreted as an endorsement of the tobacco industry.”

Source: chemistryworld.com/careers/working-in-the-tobacco-industry/3007194.article
A World Without an
“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
Noncombustible Tobacco Product Platforms

- E-Vapor
- Oral Tobacco/Nicotine Products
- Heated Tobacco Products

**E-Vapor**
- MARKTEN

**Oral Tobacco/Nicotine Products**
- Verve
- SKOAL Snus
- Copenhagen Nicotine Snuff

**Heated Tobacco Products**
- IQOS

ALCS | Willie McKinney, VP Regulatory Sciences | June 2018 | 7
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

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The Product

Exposure and Health Risk

Impact on the Population
MarkTen® Product was Designed to Eliminate or Significantly Reduce HPHC\textsuperscript{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)

\textsuperscript{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

- **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
Reduced Risk Assessment: Pre-Clinical Studies

Toxicological literature review
Individual flavors and carriers are:
- Generally recognized as safe (GRAS) for use in foods (not appropriate for inhalation)
- Food or pharmaceutical grade

Flavor Mixtures:
- 90 day *in vivo* studies

Product Specific:
- *In vitro* toxicology studies (OECD)
- Cytotoxicity and genotoxicity

1. Ingredients risk assessment
2. Carrier assessment
3. Flavor assessment
4. E-liquid and aerosol condensate
No Cytotoxicity Observed from MarkTen® Aerosol Condensates in Neutral Red Uptake Assays¹

- 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 Test¹

Ames Assay - TA98 +S9

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

Reference Cigarette 3R4F

8 MarkTen® Variants

Log Concentration/plate (mg TPM)

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

Key Takeaways:

1. Ingredients risk assessment
   - No difference compared to carrier/air control:
     - Survival & body weight
     - Clinical chemistry & hematology
     - Histopathology

2. Carrier assessment
3. Flavor assessment
4. E-liquid and aerosol condensate
   - No cytotoxicity or genotoxicity
ALCS Framework for Reduced Harm Tobacco Products

Constituent Reduction
- Product Design and Control
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The Product

Exposure and Health Risk

Impact on 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\(^1\)

\(^1\) 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

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

**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

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
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)
- Adult smokers not planning to quit (n=423)
- E-vapor users (n=426)
- Former tobacco users (n=417)
- Never tobacco users (n=425)
- Legal age to age 24 users (n=424)
- Legal age to age 24 Non-users (n=410)

- MT ranked less risky than Cig
- MT ranked equally risky as Cig
- MT ranked more risky than Cig

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)

<table>
<thead>
<tr>
<th>Product</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>14%</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>13%</td>
</tr>
<tr>
<td>Winter Mint</td>
<td>11%</td>
<td>12%</td>
<td>23%</td>
</tr>
<tr>
<td>Fusion</td>
<td>10%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Classic</td>
<td>9%</td>
<td>13%</td>
<td>19%</td>
</tr>
<tr>
<td>Blend</td>
<td>9%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Mardis Gras</td>
<td>9%</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>Harvest Blend</td>
<td>7%</td>
<td>5%</td>
<td>14%</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

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

<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>3%</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>
<td>5%</td>
<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-CM1-16-13-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 Users¹

<table>
<thead>
<tr>
<th></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® Use¹

### Switchers

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

(n=349)

### Dual Users

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

(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 Users\(^1\)

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Switchers (n=4)</th>
<th>Dual Users (n=4)</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>73%</td>
</tr>
<tr>
<td>Enjoy the taste</td>
<td>53%</td>
<td>43%</td>
</tr>
<tr>
<td>Has a flavor I like</td>
<td>46%</td>
<td>33%</td>
</tr>
<tr>
<td>To help cut back or quit smoking/using other tobacco products</td>
<td>41%</td>
<td>63%</td>
</tr>
<tr>
<td>It might be less harmful for other people around me</td>
<td>40%</td>
<td>33%</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>33%</td>
</tr>
<tr>
<td>Curiosity</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>All other reasons</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Don’t know</td>
<td>1%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Source: ALCS In-Market Adult Consumer Study – e-Cigarettes Currently Marketed as MarkTen®XL e-Vapor: A Cross-Sectional Survey of Adult MarkTen®XL e-Vapor Ever Tiers (ALCS-CMI-16-16-EV)
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
   - In-market data indicate every day use is associated with exclusive use of e-vapor

3. In market study

4. Product instruction comprehension
   - Product instructions are easily understood
ALCS Framework for Reduced Harm Tobacco Products

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- Risks and Benefits to the Population

The Product

Exposure and Health Risk

Impact on the Population
Population Assessment\(^1\)

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
- Dual User
- E-vapor User
- Former Cigarette Smoker
- Former Dual User
- Former E-vapor User

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

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\(^1\) 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

### 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>Consumer Behavior</td>
<td></td>
</tr>
<tr>
<td>Consumer Perception</td>
<td></td>
</tr>
<tr>
<td>Adverse Events</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>
<tbody>
<tr>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
</tr>
</tbody>
</table>
**Overall Conclusions**

- E-vapor products present an opportunity to reduce the harm from cigarette smoking

- Need for collaboration to advance harm reduction
  - Generate and share sound science
  - Reframe debate about nicotine
  - Truthful and accurate communications about relative risk
For additional information visit our science website at Altria.com/ALCS-Science.