Heated Tobacco Technology: Science, Behavior and Avoiding Unintended Consequences

Global Forum on Nicotine 2017

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Important Information

Reduced-Risk Products (“RRPs”) is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

We have a range of RRPs in various stages of development, scientific assessment and commercialization.

Because our RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.
Heating Tobacco Rather than Burning It

The Tobacco Heating System 2.2 (THS2.2, currently commercialized as IQOS in >25 countries) is designed and has been demonstrated to:

- Heat tobacco without combustion
- Preserve elements of the taste, sensory experience, nicotine delivery profile and ritual characteristics of cigarettes
PMI’s Scientific Assessment Approach

- Post-Market Studies and Surveillance
  - Consumer Perception and Behavior Assessment
  - Clinical Trials
- Systems Toxicology Assessment
- Standard Toxicology Assessment
- Aerosol Chemistry and Physics
- Product Design and Control Principles

- Reduced Population Harm
- Correct Understanding, Usage and impact in Different Populations
- Reduced Exposure & Risk in Humans
- Reduced Risk in Laboratory Models
- Reduced Toxicity in Laboratory Models
- Reduced Formation of Harmful and Potentially Harmful Constituents
- Absence of Combustion

Reduced Harm / Risk Concept: What We Need to Demonstrate for Tobacco Heating System

Minimize Risk to the Individual

Maximize Current Adult Smoker Acceptance and Proper Use

For Illustration Purposes Only
Reduced Formation: Rationale and Results

Measured 54 harmful and potentially harmful constituents and 4 additional analytes using validated methods in accredited facilities, both internally and at an independent laboratory.

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada list (total 47)</td>
<td>47</td>
</tr>
<tr>
<td>Smoke Constituents with established Biomarkers of Exposure</td>
<td>+2</td>
</tr>
<tr>
<td>Smoke Constituents formed &lt; 400°C</td>
<td>+4</td>
</tr>
<tr>
<td>Smoke Constituents formed &gt; 400°C</td>
<td>+5</td>
</tr>
</tbody>
</table>

THS2.2 produces an aerosol that contains on average 90-95% lower levels of harmful and potentially harmful chemicals than a reference cigarette.

Non-Clinical Evidence: Approach and Rationale

High Level Adverse Outcome Pathway of Cigarette Smoking

- Chronic Cigarette Smoke Exposure
  - Molecular changes
  - Disruption of Biological Mechanism
  - Cell / Tissue Changes
  - Physiological changes
  - Disease (CVD, COPD, Lung cancer)
  - Population Harm

Analytical Chemistry
- Biological Networks – Systems Biology/Toxicology
- Medicine
- Public Health

Biomarkers of Exposure
- Proteomics
- Transcriptomics
- Genomics
- Lipidomics
- Oxidative stress
- Inflammation
- Cell death
- Cell proliferation
- Cytology
- Differential cell count
- Gross pathology
- Histopathology
- Body weights
- Plethysmography
- Lung Function
- Atherosclerotic Plaque formation
Non-Clinical Evidence: Snapshot of Results

Mechanistic Evidence for Reduced Harm to the Lung

Non-clinical Evidence for Reduced Cardiovascular Disease Risk

THS2.2 aerosol is over 10 times less active than reference cigarette smoke in key mechanisms leading to lung damage.

In animal models, switching to THS2.2 aerosol from cigarette smoke reduces levels of cardiovascular disease risk markers to levels similar to those seen in a model of smoking cessation.
Clinical Evidence: Approach and Rationale

High Level Adverse Outcome Pathway of Cigarette Smoking

- Chronic Cigarette Smoke Exposure
- Molecular changes
  - Disruption of Biological Mechanism
  - Cell / Tissue Changes
  - Physiological changes
- Disease (CVD, COPD, Lung cancer)
- Population Harm

Analytical Chemistry

- Biomarkers of Exposure:
  - CO
  - NNN
  - NNK
  - Benzene
  - 1,3-Butadiene
  - Acrolein
  - Acrylonitrile
  - 4-ABP
  - B[a]P
  - Pyrene
  - 1-NA
  - 2-NA
  - ortho-Toluidine
  - Ethylene Oxide
  - Crotonaldehyde
- Biological Networks – Systems Biology/Toxicology
- Medicine
- Public Health

- Population Impact Modeling

- sICAM
- 11-DTX-B2
- 8-Epi-PGF2-α
- HDL
- White Blood Cell Count
- Lung Function (FEV1)
- COHb
- Total NNAL

Tobacco-related harm and disease is not defined by a single endpoint or even endpoints reflective of a single disease or biological mechanism.

In the absence of epidemiological evidence, a set of markers that are affected by smoking, are linked to smoking-related disease and are reversible after smoking cessation are required.
Clinical Evidence: Reduced Exposure

% Reduction in Biomarkers of Exposure After Switching for Three Months

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>THS2.2 vs. Cigarette</th>
<th>Cessation vs. Cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-tol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-OHP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-HPMA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total NNAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEMA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMPMA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COHb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B[a]P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-ABP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEMA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-PMA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHBMA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Levels of exposure to harmful and potentially harmful chemicals when smokers switch to THS2.2 approach the levels observed in those who quit smoking during the study.

Note: These data alone do not represent a claim of reduced risk. Source: PMI Research and Development; Registered on clinicaltrials.gov: NCT 01970995
Clinical Evidence: Favorable Changes in Smoker’s Health Profile in a 3-Month Study

<table>
<thead>
<tr>
<th>Disease Mechanisms</th>
<th>Expected Direction of Change</th>
<th>Effect of Cessation</th>
<th>Effect of Switching to THS2.2</th>
<th>Direction of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism (HDL-C)</td>
<td>Increase</td>
<td>6.4 mg/dL ↑</td>
<td>4.5 mg/dL ↑</td>
<td>Same direction as cessation</td>
</tr>
<tr>
<td>Inflammation (WBC)</td>
<td>Decrease</td>
<td>-0.40 10⁹/L ↓</td>
<td>-0.57 10⁹/L ↓</td>
<td>Same direction as cessation</td>
</tr>
<tr>
<td>Airway Impairment (FEV₁)</td>
<td>Increase</td>
<td>1.93% pred ↑</td>
<td>1.9% pred ↑</td>
<td>Same direction as cessation</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>Decrease</td>
<td>10.9 % ↓</td>
<td>8.7 % ↓</td>
<td>Same direction as cessation</td>
</tr>
<tr>
<td>(sICAM-1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxidative Stress (8-epi-PGF₂α)</td>
<td>Decrease</td>
<td>5.9 % ↓</td>
<td>12.7 % ↓</td>
<td>Same direction as cessation</td>
</tr>
<tr>
<td>Clotting (11-DTX-B₂)</td>
<td>Decrease</td>
<td>19.4 % ↓</td>
<td>9.0 % ↓</td>
<td>Same direction as cessation</td>
</tr>
</tbody>
</table>

Note: These data alone do not represent a claim of reduced risk.
Source: PMI Research and Development; Registered on clinicaltrials.gov: NCT 01970995

These studies measured the levels of 6 clinical risk markers closely associated with cardiovascular and lung disease.

Measurements of these markers in smokers who switched to THS2.2 showed that the majority of beneficial effects that were seen in the smoking cessation arm were preserved.
Adult Consumer Perception and Behavior: Approach and Results

Designed to measure Risk Perception, Comprehension and Intention to Use in a Pre-Market Setting:

- Non-intended audiences express negligible intention to use
- Adult smokers correctly understand the tested reduced risk communication
- Adult smokers correctly understand that THS2.2 is not without risk and is not an alternative to quitting
- Adult smokers react positively to the THS2.2 proposition and express sizeable intention to use
Avoiding Unintended Consequences: Dual Use, Never Smokers and Former Smokers

High rates of IQOS purchasers who have either fully or predominantly converted to the product.

Negligible interest from unintended audiences.

Results from our first launch markets show non-smokers and former smokers are not purchasing the product in large numbers.

Note: Switz. is Switzerland.
Source: Switzerland / Russia / Italy / Romania / Japan IQOS User Panels.
The data indicate that THS2.2 (IQOS) has the potential to provide a risk reduction benefit for adult smokers relative to the status quo – continued smoking. We are committed to responsible commercialization to ensure there is an overall benefit to public health. Our principles are:

**Offer the product to adult smokers who want to continue enjoying tobacco products**
- do not offer the product to people who have never smoked or who have quit smoking.

**Support adult smokers in their conversion journey through education and guidance**

**Communicate accurately and clearly to adult smokers**
- the product is **not an alternative to quitting**. The best choice for consumers concerned about the health risks of smoking is to quit tobacco products altogether.
- to experience the benefit of the product, adult smokers should **switch to it completely** and abandon cigarettes permanently.
- The product is **not risk free or a safe alternative to cigarettes**, but it is a much better choice than smoking.
Source: Philip Morris International

Acknowledgements:
Aerosol Chemistry Team – Lead: Dr. Serge Maeder
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Chief Scientific Officer – Dr. Manuel Peitsch
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