The IQOS Heating System

Tobacco Products Scientific Advisory Committee

January 24, 2018
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Introduction

Moira Gilchrist, PhD
Vice President Scientific and Public Communications
Philip Morris International
The Status Quo

Smokers

Risk Continuum

Combustibles Cessation

Highest Risk Lowest Risk

The IQOS Heating System

The IQOS Opportunity
911(g)(1) Modified Risk Products

...the applicant has demonstrated that such product, as it is actually used by consumers, will—

A. Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B. Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products
911(g)(1) Modified Risk Products

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Product Messages

Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.
Product Messages

1. Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.

2. Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.

3. Switching completely from cigarettes to the IQOS system significantly reduces your body’s exposure to harmful and potentially harmful chemicals.
Family Smoking Prevention and Tobacco Control Act

“… to provide new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry’s efforts to develop, introduce, and promote less harmful tobacco products”

-Sec. 3 (4) Purpose

Presentation Agenda

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Topic</th>
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</thead>
<tbody>
<tr>
<td>Moira Gilchrist, PhD</td>
<td>VP Scientific &amp; Public Communications</td>
<td>IQOS System and Heating Technology</td>
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<tr>
<td>Manuel Peitsch, PhD</td>
<td>Chief Scientific Officer</td>
<td>Scientific Assessment of IQOS</td>
</tr>
<tr>
<td>Antonio Ramazzotti</td>
<td>VP Human Insights and Behavioral Research</td>
<td>Perception and Behavior</td>
</tr>
<tr>
<td>Sarah Knakmuh</td>
<td>VP Heated Tobacco Products</td>
<td>U.S. Commercialization and Controls</td>
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<tr>
<td>Moira Gilchrist, PhD</td>
<td>VP Scientific &amp; Public Communications</td>
<td>Population Modeling and Conclusion</td>
</tr>
</tbody>
</table>
IQOS System and Heating Technology

Moira Gilchrist, PhD
Vice President Scientific and Public Communications
Philip Morris International

HeatStick Construction

- Mouth Piece
- Tipping Paper
- Biodegradable Film
- Hollow Acetate Tube
- Outer Paper
- Crimped Tobacco
IQOS Holder and Heating Blade

- Heating Blade
- Control Electronics
- Battery

IQOS Temperature Profile

- Combustion T°
- Programmed heater profile
- Heater turned off
- Temperature (°C)
- Time (s)
- Distance from the Blade

* Radial position of thermocouple relative to the surface of the heater
IQOS Charger

- Battery
- Electronics
- Cradle for Holder

IQOS Operation
Scientific Assessment of IQOS

Manuel Peitsch, PhD
Chief Scientific Officer
Philip Morris International

911(g)(1) Modified Risk Products

...the applicant has demonstrated that such product, as it is actually used by consumers, will—

A. Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B. Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products
Scientific Assessment

Studies
- 17 Non-Clinical Studies
- 8 Clinical Studies

Publications
- 30+ on IQOS assessment
- 150+ on assessment methods and verification

Assessment Framework: Informed by Epidemiology

The health risks of smoking are well established and supported by epidemiological evidence (IARC 2004, 2007)
The health risks of smoking and the reversal of risks after quitting smoking are well established (IARC 2004, 2007)
The health risks of switching should be lower than those of smoking. Cessation is the ‘gold standard’ for risk reduction (IOM, 2012).

Differences Between IQOS Aerosol and Cigarette Smoke

Smoke and aerosol were collected on a Cambridge filter pad using Health Canada Intense smoking regime.
IQOS Does Not Emit Carbon-Based Solid Particles

IQOS Releases Less Toxicants than Cigarettes
Non-targeted Differential Screening
Comparison of IQOS Aerosol and 3R4F Smoke

This slide presents the results for the regular variant of the IQOS HeatStick characterization.

Constituents of toxicological concern:
- Glycidol (IARC 2A)
- 2-Furanemethanol (IARC 2B)
- 3-Monochloro-1,2-propanediol (IARC 2B)
- Furfural (IARC 3)

3R4F
- ca. 4330 constituents ≥ 100 ng/stick
- ca. 3580 unique compounds in smoke

IQOS Regular
- ca. 750 constituents ≥ 100 ng/stick
- 50 constituents more abundant in IQOS than 3R4F
- 3 constituents unique to IQOS aerosol

Abundance equivalent to, or lower than, 3R4F

Exposure from IQOS is below the level of concern

Reductions of Toxicants by Disease Category

<table>
<thead>
<tr>
<th>Category</th>
<th>Reference Cigarette</th>
<th>3R4F</th>
<th>IQOS</th>
<th>Reduction</th>
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Note: Intense Health Canada’s Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine

Number of toxicants: 12, 29, 8, 18, 7
Demonstrated Reduced Emission

Study Design
Reduced Exposure in Healthy Human Subjects

Measurements: 16 Biomarkers of Exposure; Nicotine and its metabolites
Smoker Acceptance of IQOS is Similar to Cigarettes

Changes in Exposure to HPHCs with IQOS Use
Reduced Exposure in Healthy Human Subjects

* On equivalent nicotine basis
Changes in Exposure to HPHCs with IQOS Use
Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in IQOS Aerosol

Exposure is Significantly Reduced After Switching to IQOS

Carbon Monoxide

Leads to

Cigarette
IQOS

* On equivalent nicotine basis

CC-37

Changes in Exposure to HPHCs with IQOS Use
Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in IQOS Aerosol

Exposure is Significantly Reduced After Switching to IQOS

Carbon Monoxide

Leads to

Cigarette
IQOS
Smoking Abstinence

* On equivalent nicotine basis

CC-38
Changes in Exposure to HPHCs with IQOS Use
Reduced Exposure in Healthy Human Subjects

HPHCs are Drastically Reduced in IQOS Aerosol

Exposure is Significantly Reduced After Switching to IQOS

* On equivalent nicotine basis
Reduced Exposure Compared to Cigarettes
Reduced Exposure in Healthy Human Subjects

Reduced Exposure Similar to Smoking Abstinence
Reduced Exposure in Healthy Human Subjects
Switching to IQOS achieves almost 95% of the reduction achieved by smoking abstinence.

Demonstrated Reduced Exposure

- Reduced Exposure Similar to Smoking Abstinence
- Reduced Exposure in Healthy Human Subjects
  - Switching to IQOS achieves almost 95% of the reduction achieved by smoking abstinence
  - IQOS
  - Smoking Abstinence

- Reduced Exposure Similar to Smoking Abstinence
  - Smoking Abstinence
  - IQOS

- Demonstrated Reduced Exposure
  - Toxic Emissions
  - Molecular Changes
  - Disruption of Biological Mechanism
  - Cell / Tissue Changes
  - Disease
  - Population Harm

- Toxic Emissions
- Molecular Changes
- Disruption of Biological Mechanism
- Cell / Tissue Changes
- Disease
- Population Harm

- IQOS
- Toxic Emissions
- Molecular Changes
- ?
Switching Study in Apoe−/− Mouse Model

- 8 months duration (approximately 40% of lifetime)
- Concomitant analysis of CVD and COPD endpoints
- Comprehensive analysis of molecular changes and mechanistic impact
- Exposure dose corresponds to ~30 cigarettes per day in human comparison

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<th>Group</th>
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Reduced Molecular Changes in the Lung

- Proteins in Bronchoalveolar Lavage Fluid
- Gene Expression in Lung Tissue at Month 8

Reference Cigarette

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Reference Cigarette

Reduced Molecular Changes in the Lung

Proteins in Bronchoalveolar Lavage Fluid Gene Expression in Lung Tissue at Month 8

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<th>Time (months)</th>
<th>Reference Cigarette</th>
<th>IQOS Switch</th>
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* p-value <0.05

Reduced Molecular Changes in the Lung

Proteins in Bronchoalveolar Lavage Fluid

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<th>Log2Ratio</th>
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*p-value <0.05


Demonstrated Reduced Molecular Changes

- Smoking: Toxic Emissions → Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm
- Cessation: [Same process as above]
- IQOS: Toxic Emissions → [Process similar to cessation, but with a question mark indicating uncertainty]
Reduced Effects on Disease Mechanisms

Lung Inflammation

Mechanism Disruption (% ± SEM)

Time (months)

1 2 3 6 8

Cigarette

Reduced Effects on Disease Mechanisms

Lung Inflammation

Mechanism Disruption (% ± SEM)

Time (months)

1 2 3 6 8

Cigarette  IQOS Switch  Cessation
Reduced Effects on Disease Mechanisms

Lung Inflammation

Specific Markers of Lung Inflammation

Reduced Effects on Disease Mechanisms

Clinical Changes After 90 Days of Cessation
Reduced Exposure in Healthy Human Subjects
## Clinical Changes After 90 Days
### Reduced Exposure in Healthy Human Subjects

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<th>Disease Pathway</th>
<th>Endpoint</th>
<th>Abstinence Effect at 3m [95% CI]</th>
<th>Switching to IQOS Effect at 3m [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<td>HDL-C</td>
<td>0.0 mg/dL [-5.77; 5.84]</td>
<td>1.4 mg/dL [-2.35; 5.0]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
<td>-0.94 10^9/L [-2.00; 0.13]</td>
<td>0.17 10^9/L [-0.47; 0.81]</td>
</tr>
<tr>
<td>Airway Impairment</td>
<td>FEV1</td>
<td>2.0 % pred [-3.37; 7.36]</td>
<td>0.53 % pred [-2.79; 3.85]</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>sICAM-1</td>
<td>-9.9 % [-19.7; 1.1]</td>
<td>-10.6 % [-16.7; -4.0]</td>
</tr>
<tr>
<td>Oxidative Stress</td>
<td>8-epi-PGF2α</td>
<td>-8.5 % [-25.13; 11.8]</td>
<td>-13.5 % [-23.6; -1.95]</td>
</tr>
<tr>
<td>Clotting</td>
<td>11-OTX-B2</td>
<td>-7.2 % [-37.7; 38.3]</td>
<td>-3.6 % [-24.6; 23.3]</td>
</tr>
</tbody>
</table>

### Disease Pathway Endpoint

<table>
<thead>
<tr>
<th>Disease Pathway</th>
<th>Endpoint</th>
<th>Abstinence Effect at 3m [95% CI]</th>
<th>Switching to IQOS Effect at 3m [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<td>HDL-C</td>
<td>6.4 mg/dL [2.5; 10.3]</td>
<td>4.5 mg/dL [1.17; 7.88]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
<td>-0.41 10^9/L [-0.95; 0.14]</td>
<td>-0.57 10^9/L [-1.04; 0.10]</td>
</tr>
<tr>
<td>Airway Impairment</td>
<td>FEV1</td>
<td>1.94 % pred [-0.44; 4.31]</td>
<td>1.91 % pred [-0.14; 3.97]</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>sICAM-1</td>
<td>-10.9 % [-17.8; -3.4]</td>
<td>-8.7 % [-14.94; -2.05]</td>
</tr>
<tr>
<td>Oxidative Stress</td>
<td>8-epi-PGF2α</td>
<td>-5.9 % [-17.1; 6.8]</td>
<td>-12.7 % [-21.81; -2.55]</td>
</tr>
<tr>
<td>Clotting</td>
<td>11-OTX-B2</td>
<td>-19.4 % [-30.1; -7.0]</td>
<td>-8.98 % [-19.52; 2.94]</td>
</tr>
</tbody>
</table>

---

## Demonstrated Reduced Disruption of Biological Mechanisms

- **Smoking Cessation**
  - Toxic Emissions Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm
- **IQOS**
  - Toxic Emissions Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease (?)
Reduces the Effects on Cells

Inflammatory Lung Cells in Bronchoalveolar Lavage Fluid

Reduces the Effects on Tissues

Lung Tissue Destructive Index
Demonstrated Reduced Cell & Tissue Changes

Smoking
- Toxic Emissions
- Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

Cessation
- Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

IQOS
- Toxic Emissions
- Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease

Reduces the Risk of Disease in vivo

Disease Endpoint for COPD
- Lung Emphysema
- Data from Histology after 8 months

Time (months)
0 1 2 3 6 8
0 1 2 3 4 5
Emphysema Score
Mean ± SEM
Fresh Air Cigarette IQOS Switch Cessation IQOS

Reduces the Risk of Disease in vivo

Disease Endpoint for CVD
Atherosclerotic Plaque in the Aortic Arch
Data from μCT at month 7

Plaque surface area (mm²)
Aorta mean occlusion (%)
Plaque volume (mm³)

Mean ± SEM

Fresh Air  Cigarette smoke  IQOS Switch  Cessation  IQOS

How Cigarette Smoke Causes Cancer

Genetic damage
"the match that lights the fire"**

Inflammation
"fuel that feeds the flames"*

Questions
Does switching from cigarettes to IQOS
1. Reduce Genetic damage?
2. Reduce Inflammation?
3. Reduce the risk of lung cancer?

Carcinogens
Nanoparticles**
HPHCs

Tumor initiation
Cancer

Tumor progression & Invasiveness***

Genetic Damage is Reduced by IQOS

Does Switching to IQOS Reduce Genetic damage?

Genetic damage
"the match that lights the fire"*

Carcinogens

Tumor initiation

Evidence from IQOS Assessment

Reduced Emission of Carcinogens

Reduced Exposure to Carcinogens

Reduced DNA Damage

Reduced Genotoxicity

Reduced Exposure Response

Reduced Genetic Damage


Nanoparticles Deposit in the Lung

Cigarette Smoke
Carbon-based nanoparticles
6x10^{11} particles \approx 0.7 mg

IQOS Aerosol
No solid particles

Cigarette smoke (600 mg/m^{3} TPM)

Lung Deposition after 6 months

Corresponding concentration of IQOS aerosol

ApoE-/- mice exposed for 6 months, 3h/day and 5days/week.
**Inflammatory Markers in Smokers’ Lungs**

Table 2. Mean bronchoalveolar lavage (BAL) cell concentrations in smokers and nonsmokers

<table>
<thead>
<tr>
<th>Cell type</th>
<th>BAL concentration x10^6 cells·ml^{-1}</th>
<th>F statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smokers (n=14)</td>
<td>Nonsmokers (n=16)</td>
<td></td>
</tr>
<tr>
<td>Macrophage</td>
<td>524±219</td>
<td>220±98</td>
<td>25.1</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>12±9.13</td>
<td>2.1±1.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>7.3±1.7</td>
<td>14.8±1.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>0.9±1.7</td>
<td>1.1±1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Epithelial</td>
<td>1.5±1.4</td>
<td>2.1±2.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD. Statistics quoted are by discriminant analysis. Overall model Hotelling’s statistic = 1.7; p=0.0001. Critical Bonferroni alpha (n tests=5) = 0.01.

**Inflammation and Cancer**

**The Role of Interleukin-1β in Cancer**

**Animal Studies**

**Human Study (CANTOS)**

<table>
<thead>
<tr>
<th>Lung Metastases (%)</th>
<th>Placebo</th>
<th>Canakinumab 50mg</th>
<th>Canakinumab 150mg</th>
<th>Canakinumab 300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI) p</td>
<td>1.0 (ref)</td>
<td>0.74 (0.47-1.17)</td>
<td>0.61 (0.39-0.97)</td>
<td>0.33 (0.18-0.59)</td>
</tr>
</tbody>
</table>

p trend across groups <0.0001

* Voronov et al. IL-1β is required for tumor invasiveness and angiogenesis. PNAS 2002; 100:2645-2650.
Evidence from IQOS Assessment

- Reduced Emission of HPHCs and No carbon-based nanoparticles
  - Reduced Exposure to HPHCs
  - No Exposure to nanoparticles

- Reduced Lung Inflammation

Does Switching to IQOS Reduce Inflammation?

- Inflammation "fuel that feeds the flames"
- Nanoparticles**
- HPHCs

Tumor progression & Invasiveness***

Evidence from IQOS Assessment: Does Switching to IQOS Reduce Inflammation?

- Reduced Emission of HPHCs and No carbon-based nanoparticles
  - Reduced Exposure to HPHCs
  - No Exposure to nanoparticles

- Reduced Lung Inflammation

Summary of Totality of Evidence

IQOS
Toxic Emissions

Exposure
Molecular Changes
Disruption of Biological Mechanism
Cell / Tissue Changes
Disease

90-95% less Toxicants
90-95% of Abstinence
90-95% of Cessation
90-95% of Cessation
90-95% of Cessation

Population Harm

Demonstrate a Benefit to the Health of the Population as a Whole …
Consumer Perception and Behavior

Antonio Ramazzotti
Vice President Human Insights and Behavioral Research
Philip Morris International

911(g)(1) Modified Risk Products

...the applicant has demonstrated that such product, as it is actually used by consumers, will—

A. Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B. Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products
### Who Will Use IQOS and to What Degree?

<table>
<thead>
<tr>
<th>Adult Smokers</th>
<th>Non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Understanding of Messages</strong></td>
<td><strong>Understanding of Messages</strong></td>
</tr>
<tr>
<td><strong>Intent to Use</strong></td>
<td><strong>Increased or Decreased Likelihood of Initiation</strong></td>
</tr>
<tr>
<td><strong>Exclusive Use</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Increased or Decreased Likelihood of Cessation</strong></td>
<td></td>
</tr>
</tbody>
</table>

**PBA Studies to Develop and Assess IQOS Messages**

**Phase 1**
- Developing the most appropriate product messages
  - Comprehension
  - Intent to Use
  - Risk Perception

**Phase 2**
- Assessing Labeling and Advertising
  - Comprehension
  - Intent to Use
  - Risk Perception

6 qualitative and quantitative studies to develop and assess IQOS communications

3 Studies

3 Studies
Product Messages (On a Tested Pack)

1. Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.
2. Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.
3. Switching completely from cigarettes to the IQOS system significantly reduces your body’s exposure to harmful and potentially harmful chemicals.

Study Design
IQOS Communication Studies

Five arms, experimental studies, describing responses to materials on comprehension, intent to use, change in intention to quit and risk perception

≈ 2,200 enrolled participants in each study
• Five subject groups: adult smokers with and without intention to quit, adult former smokers, adult never smokers and LA-25 Adult Never Smokers
• Sample was balanced, by subject group, sex, age group and city

Conducted in 4 US cities
Tested Product Message
Reduced Risk of Harm

HeatSticks Pack with SG’s Warnings

AVAILABLE EVIDENCE TO DATE:
Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.

SURGEON GENERAL’S WARNING:
Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.

HeatSticks Pack with PMI Warning

AVAILABLE EVIDENCE TO DATE:
Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.

IMPORTANT WARNING:
- Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. HeatSticks™ contain nicotine, which is addictive.

The Majority Understood that IQOS Presents Less Risk of Harm, but is Not Risk Free

IQOS Communication Study - Reduced Risk of Harm

- HeatSticks Pack PMI Warning n=380
- HeatSticks Pack SG’s Warnings n=376

Correct Comprehension | Less risk of harm (correct)
----------------------|----------------------
78%                   | 73%

0% 20% 40% 60% 80% 100%
Only 1% and 2% Misunderstood that IQOS Presents “No Risk of Harm”

IQOS Communication Study - Reduced Risk of Harm

Correct Comprehension | Less risk of harm (correct) | The same risk of harm | Greater risk of harm | No risk of harm | Don’t know

- HeatSticks Pack PMI Warning n=380
- HeatSticks Pack SG’s Warnings n=376

Substantial Intention to Use IQOS Among Adult Smokers with No Intention to Quit

IQOS Communication Study - Reduced Risk of Harm

- HeatSticks Pack SG’s Warnings
- HeatSticks Pack PMI Warning

* Error bars show 95% confidence intervals for the ‘very likely’ and ‘definitely’ categories combined.
Study Design
Actual Use Study

Single group, observational study, *ad libitum* use of IQOS and cigarettes, reported on a stick-by-stick basis

1,336 enrolled participants
Quota sampling approximating the distribution of US adult smokers population by sex, age, race and income (CDC, 2012)

Conducted in 8 US geographic areas

1-week baseline, 6-week observational and 1-week close out period

15% of U.S. Adult Daily Smokers Switched from Cigarettes to IQOS

IQOS and Cigarettes Use: Observational Period
Actual Use Study

% of Participants by Use Categories

- Exclusive Use: [95-100]% IQOS
- Predominant Use: [70-95]% IQOS
- Combined Use: [30-70]% IQOS
- Cigarette Use: [0-30]% IQOS

Week 1 (n=1,106) Week 2 (n=1,061) Week 3 (n=1,038) Week 4 (n=1,009) Week 5 (n=997) Week 6 (n=968)
No Increase in IQOS and Cigarettes Consumption Between Baseline and Observational Period

Actual Use Study: IQOS + Cigarette Consumption

Exclusive or Predominant IQOS Use

Combined IQOS Use

Between 12% and 30% of Participants Switched to IQOS

IQOS Usage Patterns
Post-market Data Show Exclusive Use is the Most Common Behavior Among IQOS Purchasers

![Bar chart showing usage categories in Japan and Italy]

Japan (n=6,925)
- Exclusive Use: 72%
- Predominant Use: 9%
- Combined Use: 11%
- Cigarette Use: 8%

Italy (n=4,197)
- Exclusive Use: 61%
- Predominant Use: 13%
- Combined Use: 11%
- Cigarette Use: 15%

Increased Awareness and Repeated Communication Lead to Higher Switching Rates

![Bar chart showing exclusive use at week 3 by month of IQOS purchase in Japan]

Exclusive Use at Week 3 by Month of IQOS Purchase - Japan

- Sept 2015: 35%
- Nov 2015: 49%
- Jan 2016: 56%
- Mar 2016: 61%

Source: Consumer Panel Japan, March 2016
Who Will Use IQOS and to What Degree?

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<td><strong>Likelihood of Cessation</strong></td>
<td></td>
</tr>
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</table>

Minimal Interference on Intention to Quit All Tobacco among Adult Smokers with the Intention to Quit

- HeatSticks Pack SG’s Warnings
  - Pre-Exposure: 84% (n=96)
  - Post-Exposure: 82% (n=96)

- HeatSticks Pack PMI Warning
  - Pre-Exposure: 87% (n=94)
  - Post-Exposure: 90% (n=94)
Low Levels of Intent to Use Among Adult Never Smokers and LA-25 Never Smokers

IQOS Communication Study - Reduced Risk of Harm

Adult Never Smokers
Positive "Intention to Try"

Legal Age to 25 Years Never Smokers
Positive "Intention to Try"

Positive Intention to Try IQOS is the sum of % Very Likely and % Definitely responses
Error bars show 95% confidence intervals for the 'very likely' and 'definitely' categories combined

CC-91

Low Levels of Intent to Use Among Adult Former Smokers

IQOS Communication Study - Reduced Risk of Harm

Adult Former Smokers
Positive "Intention to Try"

Positive Intention to Try IQOS is the sum of % Very Likely and % Definitely responses
Error bars show 95% confidence intervals for the 'very likely' and 'definitely' categories combined

CC-92
911(g)(1) Modified Risk Products

...the applicant has demonstrated that such product, as it is actually used by consumers, will—

A. Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B. Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products

U.S. Commercialization and Controls

Sarah Knakmuhs
Vice President, Heated Tobacco Products
Philip Morris USA
Tobacco Harm Reduction in the U.S.

“For the first time...the federal government
...is able to bring science-based regulation
to the manufacturing, marketing, and
distribution of tobacco products.”

- Former FDA Commissioner Margaret A. Hamburg, M.D., September 19, 2013

IQOS in the U.S.
Behavior Change – IQOS Use

- Device Usability
- Charging & Cleaning
- Taste & Experience

PM USA Marketing Approach for IQOS

Objective

<table>
<thead>
<tr>
<th>Awareness</th>
<th>Trial</th>
<th>Conversion</th>
</tr>
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<tbody>
<tr>
<td>Introduce IQOS</td>
<td>Explain Product &amp; Encourage Trial</td>
<td>Support Exclusive Switching</td>
</tr>
</tbody>
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Intended Audience = U.S. Adult Smokers
Build Awareness for IQOS

- Print Advertising
- Direct Mail
- Email

Electronic Age Verification

- **Data Entry**: Consumer inputs data for age and identity
- **Validation**: Match inputs with identity on electronic databases
- **Authentication**: Consumer answers questions to confirm identity
Opportunities for Trial of IQOS

Individual Engagements

Consumer Events

Retail

Trial of IQOS

Verification
Confirm age and identity via government issued ID

Confirmation
Confirm smoking status

Guided Trial
Provide overview and perform guided trial
IQOS Support

Device Troubleshooting
HeatStick Availability
Personal Support

PM USA Marketing Approach for IQOS

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<table>
<thead>
<tr>
<th>Examples</th>
<th>Direct Mail</th>
<th>Consumer Events</th>
<th>Customer Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Print Media</td>
<td>Retail Engagement</td>
<td>Personal Support</td>
<td></td>
</tr>
</tbody>
</table>

Intended Audience = U.S. Adult Smokers

CC-103

CC-104
Post-market Surveillance

**Surveillance**
- U.S. call center
- IQOS product safety summary
- Literature reviews
- Regulatory reporting systems (FDA/HHS/WHO)
- National poison data system

**Adverse Events**
- Product Misuse

**Studies**
- Cross-sectional surveys
- Longitudinal cohort study

**Consumer Perception & Behavior**
- Self-Reported Health Measures*

*For Longitudinal Cohort Study

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**IQOS in the U.S.**

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Population Modeling and Conclusion

Moira Gilchrist, PhD
Vice President Scientific and Public Communications
Philip Morris International

The PMI Population Health Impact Model

Prevalence Component

Epidemiological Risk Component


The Prevalence Component

Hypothetical population based on publicly available databases and scientific literature
Transition probabilities

Validated using published smoking statistics

The Epidemiological Risk Component

Hypothetical population risk estimates
Ischemic heart disease, lung cancer, stroke, and COPD

Validated using estimates from the Surgeon General’s Report
The PMI Population Health Impact Model

Prevalence Component

Epidemiological Risk Component

Modeling Simulations

Mortality Impact Estimates

Benefit to the U.S. Population as a Whole

90% of cessation benefit
15% switching

90,155 Smoking-related deaths averted

References:
**911(g)(1) Modified Risk Products**

...the applicant has demonstrated that such product, as it is actually used by consumers, will—

A. Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users

B. Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products

**The IQOS Opportunity**

[Image of IQOS device]
The IQOS Opportunity

• Millions fewer smokers
• Reduced harm and tobacco-related disease
• An important step forward

The IQOS Heating System

Tobacco Products Scientific Advisory Committee
January 24, 2018
Non-targeted Differential Screening
Comparison of IQOS Aerosol and 3R4F Smoke

This slide presents the results for the regular variant of the IQOS HeatStick characterization.

**3R4F**
- ca. 4330 constituents ≥ 100 ng/stick

**IQOS Regular**
- ca. 750 constituents ≥ 100 ng/stick

- Abundance equivalent to, or lower than, 3R4F

- 3 constituents unique to IQOS aerosol

- 50 constituents more abundant in IQOS than 3R4F

Constituents of toxicological concern:
- Glycidol (IARC 2A)
- 2-Furanemethanol (IARC 2B)
- 3-Monochloro-1,2-propanediol (IARC 2B)
- Furfural (IARC 3)
Results

Ames: IQOS Regular

- TPM from IQOS Regular is not mutagenic
- TPM from 3R4F is mutagenic in the presence of S9 in TA98, TA100, and TA1537

Results

Mouse Lymphoma Assay (MLA) - IQOS Regular

Relative Mutagenicity expressed as lowest observable genotoxic effect levels (LOGELs)
Summary of Demographics and Subject Characteristics – Main Sample: Race, Ethnicity and Education Level
IQOS Communication Study (Reduced Risks of Harm Claim)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>292 (77.7)</td>
<td>288 (77.0)</td>
<td>281 (75.5)</td>
<td>287 (75.5)</td>
<td>286 (76.7)</td>
<td></td>
</tr>
<tr>
<td>Black, n(%)</td>
<td>60 (16.0)</td>
<td>57 (15.2)</td>
<td>64 (17.2)</td>
<td>63 (16.6)</td>
<td>65 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Asian, n(%)</td>
<td>5 (1.3)</td>
<td>6 (1.6)</td>
<td>4 (1.1)</td>
<td>5 (1.3)</td>
<td>2 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>19 (5.0)</td>
<td>23 (6.1)</td>
<td>24 (6.4)</td>
<td>25 (6.6)</td>
<td>20 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Missing, n</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino, n (%)</td>
<td>52 (13.8)</td>
<td>55 (14.7)</td>
<td>51 (13.7)</td>
<td>64 (16.8)</td>
<td>46 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino, n (%)</td>
<td>324 (86.2)</td>
<td>319 (85.3)</td>
<td>322 (86.3)</td>
<td>316 (83.2)</td>
<td>327 (87.7)</td>
<td></td>
</tr>
<tr>
<td>Missing, n</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some high school or less, n (%)</td>
<td>18 (4.8)</td>
<td>25 (6.7)</td>
<td>13 (3.5)</td>
<td>21 (5.5)</td>
<td>9 (2.4)</td>
<td></td>
</tr>
<tr>
<td>High school graduate, n (%)</td>
<td>56 (14.6)</td>
<td>39 (10.4)</td>
<td>54 (14.5)</td>
<td>57 (15.0)</td>
<td>58 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Some college, n (%)</td>
<td>134 (35.6)</td>
<td>156 (41.7)</td>
<td>147 (39.4)</td>
<td>148 (38.9)</td>
<td>147 (39.4)</td>
<td></td>
</tr>
<tr>
<td>College graduate, n (%)</td>
<td>132 (35.1)</td>
<td>119 (31.8)</td>
<td>125 (33.5)</td>
<td>129 (33.9)</td>
<td>124 (33.2)</td>
<td></td>
</tr>
<tr>
<td>Advanced degree, n (%)</td>
<td>37 (9.8)</td>
<td>35 (9.4)</td>
<td>34 (9.1)</td>
<td>25 (6.6)</td>
<td>35 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Missing, n</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

How HeatSticks are Consumed According to “Usage Categories”: By Product Types Used (Menthol, Regular)
Actual Use Study

- **Exclusive Use:** [95-100]% IQOS
- **Predominant Use:** [70-95]% IQOS
- **Combined Use:** [30-70]% IQOS
- **Cigarette Use:** [0-30]% IQOS
IQOS HeatStick Pack (RRC2)

IQOS and Cigarettes Use: End of the Observational Period
Whole Offer Test Studies

South Korea (n=843) Japan (n=638) Germany (n=377) Italy (n=535) Switzerland (n=416)

Exclusive Use: [95-100%] IQOS
Predominant Use: [70-95%] IQOS
Combined Use: [30-70%] IQOS
Cigarette Use: [0-30%] IQOS

Total in any specific week could be lower than 100% given “no CC or Tobacco Sticks use” option WOT
IQOS In Market Usage Patterns
Post-Market Consumer Panel Surveys

Consumer Panel Surveys. August 2017

Exposures Are Below the Levels of Concern from in vivo Studies

<table>
<thead>
<tr>
<th>Compound</th>
<th>Quantities in IQOS Aerosol [µg/Stick]</th>
<th>IARC Class</th>
<th>Exposure level without tumors in vivo</th>
<th>Delivered dose in vivo [µg/kg/day]</th>
<th>Human Equivalent Concentration (HEC)² [µg/kg/day]</th>
<th>Ratio IQOS/HEC exposure to 40 Sticks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycidol¹</td>
<td>5.71</td>
<td>2A</td>
<td>3 ppm</td>
<td>0.896</td>
<td>144.6</td>
<td>1/39</td>
</tr>
<tr>
<td>2-Furanemethanol²</td>
<td>39.18</td>
<td>2B</td>
<td>2 ppm</td>
<td>0.499</td>
<td>80.5</td>
<td>1/3</td>
</tr>
<tr>
<td>3-Monochloro-1,2-propanediol</td>
<td>9.94</td>
<td>2B</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Furfural³</td>
<td>31.08</td>
<td>3</td>
<td>400 ppm</td>
<td>89.539</td>
<td>12099.9</td>
<td>1/584</td>
</tr>
</tbody>
</table>

NA: No inhalation toxicity data available, but positive in Ames test

## IQOS Transition Matrix

### Post-Market Consumer Panel Survey in Japan

### Transition Matrix

<table>
<thead>
<tr>
<th>Use in Week 1-3 (% Row)</th>
<th>Use in Week 10-12</th>
<th>Exclusive [95-100% IQOS]</th>
<th>Predominant [70-95% IQOS]</th>
<th>Situational [5-70% IQOS]</th>
<th>Abandoner [0-5% IQOS]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exclusive</strong> [95-100% IQOS]</td>
<td></td>
<td>80%</td>
<td>13%</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Predominant</strong> [70-95% IQOS]</td>
<td></td>
<td>63%</td>
<td>24%</td>
<td>12%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Situational</strong> [5-70% IQOS]</td>
<td></td>
<td>28%</td>
<td>13%</td>
<td>52%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Abandoner</strong> [0-5% IQOS]</td>
<td></td>
<td>11%</td>
<td>9%</td>
<td>14%</td>
<td>66%</td>
</tr>
</tbody>
</table>

---

## PM USA Marketing Approach for IQOS

### Objective

- **Introduce IQOS**
- **Explain Product & Encourage Trial**
- **Support Exclusive Switching**

### Examples

- **Awareness**
  - Introduce IQOS
  - Direct Mail
  - Print Media

- **Trial**
  - Explain Product & Encourage Trial
  - Consumer Events
  - Retail Engagement

- **Conversion**
  - Support Exclusive Switching
  - Customer Care
  - Personal Support

**Intended Audience = U.S. Adult Smokers**
Retail

Entry
Confirm age and identity via government issued ID

Guided Trial
Confirm smoking status

Purchase
Register for Database and Support

Impact of Dual Use
3 months Reduced Exposure Study in the US

Robust Exposure Reduction following IQOS use at 3 month in all analysis populations.

% Reduced Exposure in IQOS vs. Smoking

- Compliant
- Per Protocol
- Full Analysis Set

3-hydroxypropylmercapturic acid (3-HPMA), Monohydroxybutenyl mercapturic acid (MHBMA), and S-phenylmercapturic acid (S-PMA) in 24-hour urine (concentration adjusted for creatinine), and carboxyhemoglobin (COHb) in blood

UC-87

DP-8
No Increase in IQOS and Cigarettes Consumption Between Baseline and Observational Period

Actual Use Study: IQOS + Cigarette Consumption

Exclusive IQOS Use
n=73

Predominant IQOS Use
n=68

Baseline Observational Consumption (Stick/Day)

# of IQOS # of Cigarettes

Selection of Study Population
Actual Use Study

Inclusion Criteria: Each subject had to meet the following criteria to be eligible for the study:

a) 18 years of age or above according to the minimum LA, whichever was higher
b) Current daily smokers of regular and/or menthol CC with no intention of quitting within the next 30 days
A current daily smoker was defined as an individual who had smoked at least 100 cigarettes in his/her lifetime and was currently smoking at least 1 regular or menthol CC (no brand restrictions) per day (disregarding religious fasting). Participants who intended to quit smoking within the next 30 days were excluded from the study, because they did not intend to remain smokers for the entire duration of the study
c) Individuals who signed an ICF and were able to understand the information provided in the ICF
d) Individuals available and interested in participating in an 8 week study about tobacco
e) Individuals with positive intention to use the iQOS system
f) Individuals currently living in the United States (US)

Exclusion Criteria: Subjects who met any of the following criteria were excluded from the study:

a) Pregnant or breastfeeding women (based on self-reported status)
b) Women of childbearing potential who were not using adequate means of contraception (self-reported)
c) Individuals with no proof of age (photo identity document (ID), such as passport, driver’s license)
d) Individuals who had started smoking within the last 30 days
e) Individuals who were not able to read and speak English
f) Individuals employed in the fields of market research, marketing, advertising, media or journalism, law, manufacturers or distributors of tobacco products, or who were health care providers
g) Individuals who had taken part in a consumer or clinical study within the past 3 months
**Extent of Exposure to Investigational Product (PP)**

![Bar chart showing the extent of exposure to investigational product.](SD-1135)

**Product Use Per Day – IQOS and CC**

![Bar chart showing product use per day for IQOS and CC.](TC-52)

REXC-03, REXC-04: Studies with 5 Days of Exposure in Confinement
REXA07, REXA08: 3 Month Reduced Exposure Studies in an Ambulatory Setting
BoExp Ratios – Day 90
3 Months Reduced Exposure Study in an Ambulatory Setting (US)

Ratios BoExp ZRHM-REXA-08-US (PP)
Day 90

Percent ± 95% CI

- All IQOS users : CC
- upper 25% IQOS users : CC
- SA : CC

TC-58