

## Tobacco Heating System 2.2, A Candidate Modified Risk Tobacco Product: Cardiovascular Disease Risk Assessment

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#### **Important Information**



Reduced-Risk Products ("RRPs") is the term PMI uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes.

PMI's RRPs are in various stages of development and commercialization outside the United States in a number of countries, and we are conducting extensive and rigorous scientific studies to determine whether we can support claims for such products of reduced exposure to harmful and potentially harmful constituents in smoke, and ultimately claims of reduced disease risk, when compared to smoking cigarettes.

Before making any such claims, we will rigorously evaluate the full set of data from the relevant scientific studies to determine whether they substantiate reduced exposure or risk.

Any such claims may also be subject to government review and authorization, as is the case in the United States today.

### **Individual and Population Benefit**

Smoking is a major risk factor for Cardiovascular Disease and Stroke, with almost one third of deaths of Coronary Heart Disease are attributable to smoking and secondhand smoke exposure.\*



It is estimated that more than 1 billion people will continue to smoke for the foreseeable future\*\*\*

Successful harm reduction requires a range of scientifically substantiated, noncombustible Reduced-Risk Products that are acceptable to current adult smokers who do not quit as alternatives to cigarettes.

Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)

Note Reduced-Risk Products ("RRPs") is the term PMI uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes

\* Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association

\*\* Benowitz, N. L. and A. D. Burbank (2016). Cardiovascular toxicity of nicotine: implications for electronic cigarette use. Trends Cardiovasc Med, in press

\*\*\* http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html



# Heating Tobacco Rather than Burning It

The Tobacco Heating System 2.2 (THS2.2, commercialized as *iQOS* in several countries) is designed and has been demonstrated to:

- Heat tobacco without combustion
- Significantly reduce or eliminate the formation of harmful and potentially harmful compounds
- Preserve elements of the taste, sensory experience, nicotine delivery profile and ritual characteristics of cigarettes





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#### **Developing Scientific Evidence: PMI's Assessment of THS2.2**



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#### Laboratory Studies Demonstrate Reduced Formation



Average reductions in the formation of harmful and potentially harmful chemicals for THS2.2 compared to levels measured in smoke from the 3R4F reference cigarette<sup>(a)</sup>



THS2.2 does not combust tobacco and produces an aerosol that contains on average 90-95% lower levels of harmful and potentially harmful chemicals than a reference cigarette.

Photographs of

the Cambridge filter pads after

the collection of:cigarette

smoke (top)

 THS2.2 aerosol (bottom)

and:

(a) Aerosol collection with Intense Health Canada's Smoking Regime: 55 mL puff volume, 2-second puff duration, 30-second interval puff. Comparison on a per-stick basis. Reduction calculations exclude Nicotine, Glycerin and Total Particulate Matter
 (b) The PMI 58 list includes the FDA 18 and (c) the 15 carcinogens of the IARC Group 1
 Note: These data alone do not represent a claim of reduced exposure or risk



#### Clinical Studies in Smokers Demonstrate Reduced Exposure



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

#### Laboratory Models Show Reduced Activity in Cellular Mechanisms of Disease





THS2.2 aerosol is over 10 times less active than reference cigarette smoke in key mechanisms leading to atherosclerotic plaque formation and endothelial cell dysfunction, which are important in cardiovascular disease development



Note: These data alone do not represent a claim of reduced exposure or reduced risk.

Ref: Poussin, C., A. et al (2016). Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. Toxicology 339: 73-86.

#### Laboratory Models Demonstrate Favorable Changes in Disease Related Endpoints



State-of-the-art *in vivo* laboratory models, developed to predict cardiovascular disease risk, also demonstrate that switching to THS2.2 from cigarette smoke reduces levels of cardiovascular disease risk markers to levels similar to smoking cessation, the gold standard<sup>\*</sup> for disease risk reduction.



Note: These data alone do not represent a claim of reduced exposure or reduced risk. CVD is cardiovascular disease. Switching is switching to THS2.2 Source: \*IOM (Institute of Medicine), 2012, Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, DC: The National Academies Press Ref: Phillips, B., E. et al (2016). An 8-month systems toxicology inhalation/cessation study in Apoe-/- mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with conventional cigarettes. Toxicol Sci 149(2): 411-432.

#### **Clinical Studies Demonstrate Favorable Changes in Smoker's Health Profile**



Disease Mechanisms	Expected Direction of Change	Effect of Cessation	Effect of Switching to THS2.2	Direction of Change
Lipid Metabolism (HDL-C)	Increase	6.4 mg/dL 🛧	4.5 mg/dL 🛧	Same direction as cessation
Inflammation (WBC)	Decrease	-0.40 10 <sup>9</sup> /L 🖊	-0.57 10 <sup>9</sup> /L 🕹	Same direction as cessation
Endothelial Dysfunction (sICAM-1)	Decrease	10.9 % 🕹	8.7 % 🗸	Same direction as cessation
Oxidative Stress (8-epi-PGF <sub>2α</sub> )	Decrease	5.9 % 🗸	12.7 % 🗸	Same direction as cessation
Clotting (11-DTX-B <sub>2</sub> )	Decrease	19.4 % 🗸	9.0 % 🗸	Same direction as cessation

These studies measured the levels of 5 clinical risk markers closely associated with cardiovascular 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.



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

### **Clinical Studies Demonstrate Product Acceptability – Verified in Commercialization**





Source: PMI Research and Development; Registered on clinicaltrials.gov: NCT 01970995; NCT 01989156

In 3-month clinical studies in Japan and the US, THS2.2 provided similar levels of smoking satisfaction as the participants' own cigarette.

Commercialization results confirm product acceptability.

In Japan at least 100,000 smokers have switched to THS2.2 (commercialized as *iQOS*), representing a full conversion rate of 48%.



#### The Potential of THS2.2 to Contribute to Tobacco Harm Reduction



The data indicate that THS2.2 has the potential to provide a risk reduction benefit for adult smokers relative to the status quo – continued smoking:

- levels of exposure to harmful or potentially harmful compounds when smokers switch to THS2.2
  approach the levels observed in those who quit smoking during the study;
- THS2.2 aerosol is over **10 times less active** than reference cigarette smoke **in key mechanisms** associated with cardiovascular disease;
- switching to THS2.2 from cigarettes produces favorable changes in endpoints related to cardiovascular disease, achieving the majority of the effects that were seen in smoking cessation;
- THS2.2 provided **similar levels of smoking satisfaction** as the participants own cigarette.

The **totality-of-the-evidence** collected relating to THS2.2 to-date is very **encouraging**. PMI intend to submit a Modified Risk Tobacco Product Application to the U.S. FDA by the end of 2016.



### **Independent Verification of PMI's Results**

A multi-year program to obtain independent verification of our data and conclusions has been in place since 2011, including:



Verifying scientific methods and results using a crowd-sourcing collaborative approach, open to all experts

www.sbvimprover.com



to verify specific data sets and conclusions (e.g. absence of combustion) with independent experts

www.pmiscience.com

#### INVESTIGATOR INITIATED STUDIES PROGRAM

Promote and support investigator initiated studies that independently advance scientific/medical knowledge or verify PMI science for our developed and commercialized RRPs

www.pmiscience.com



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#### Source: Philip Morris International R&D

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