



PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

Clinical assessment of products aiming at reducing the risk of use compared with continued cigarette smoking

April 26th 2018

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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 products do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

Offering adult smokers products that reduce risk

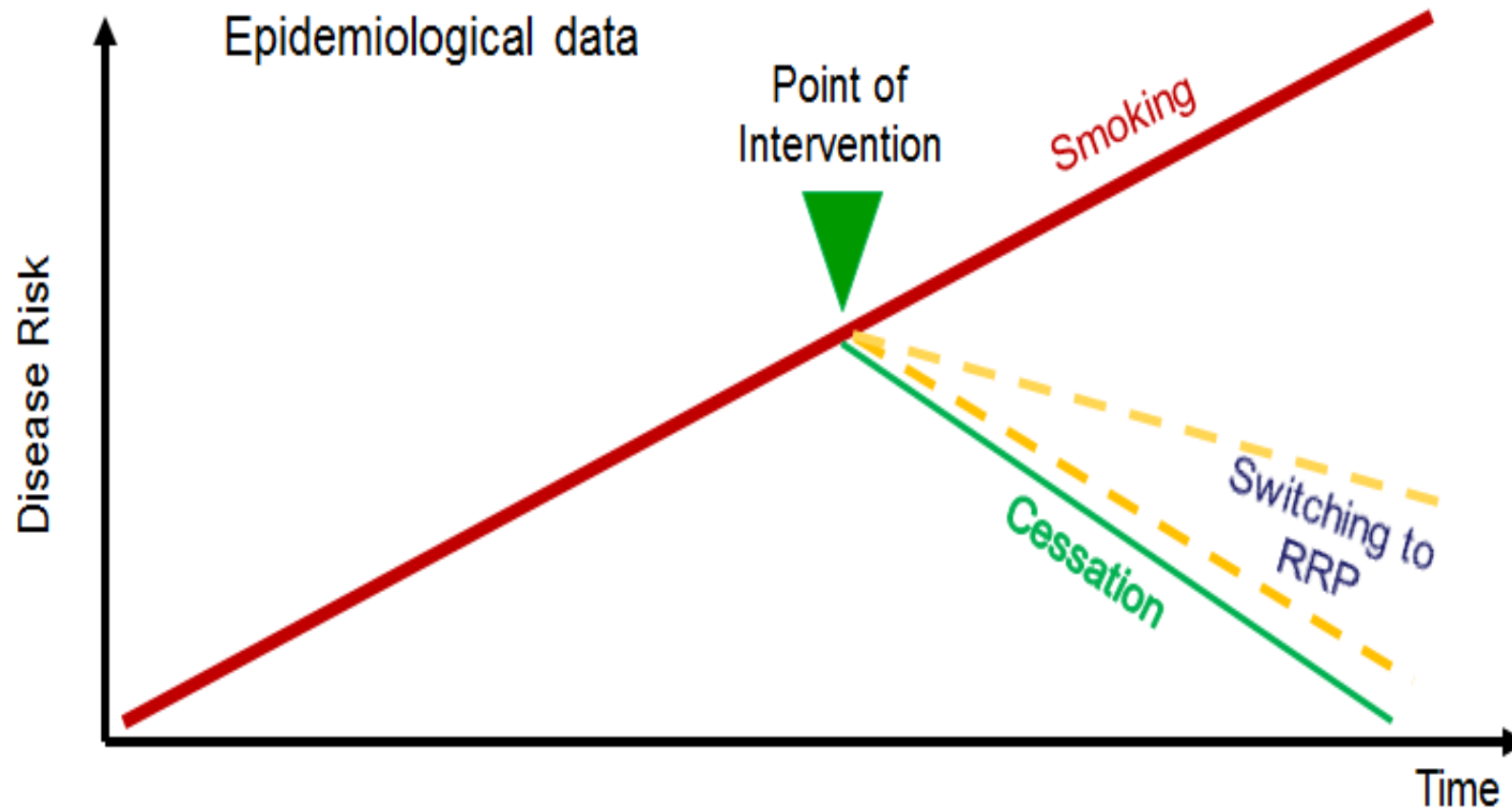
- Smoking is addictive and causes a number of serious diseases
- Worldwide, it is estimated that more than **1 billion people** will continue to smoke in the foreseeable future*



- Our ambition is to lead a full-scale effort to ensure that non-combustible products ultimately replace cigarettes to the benefit of adult smokers

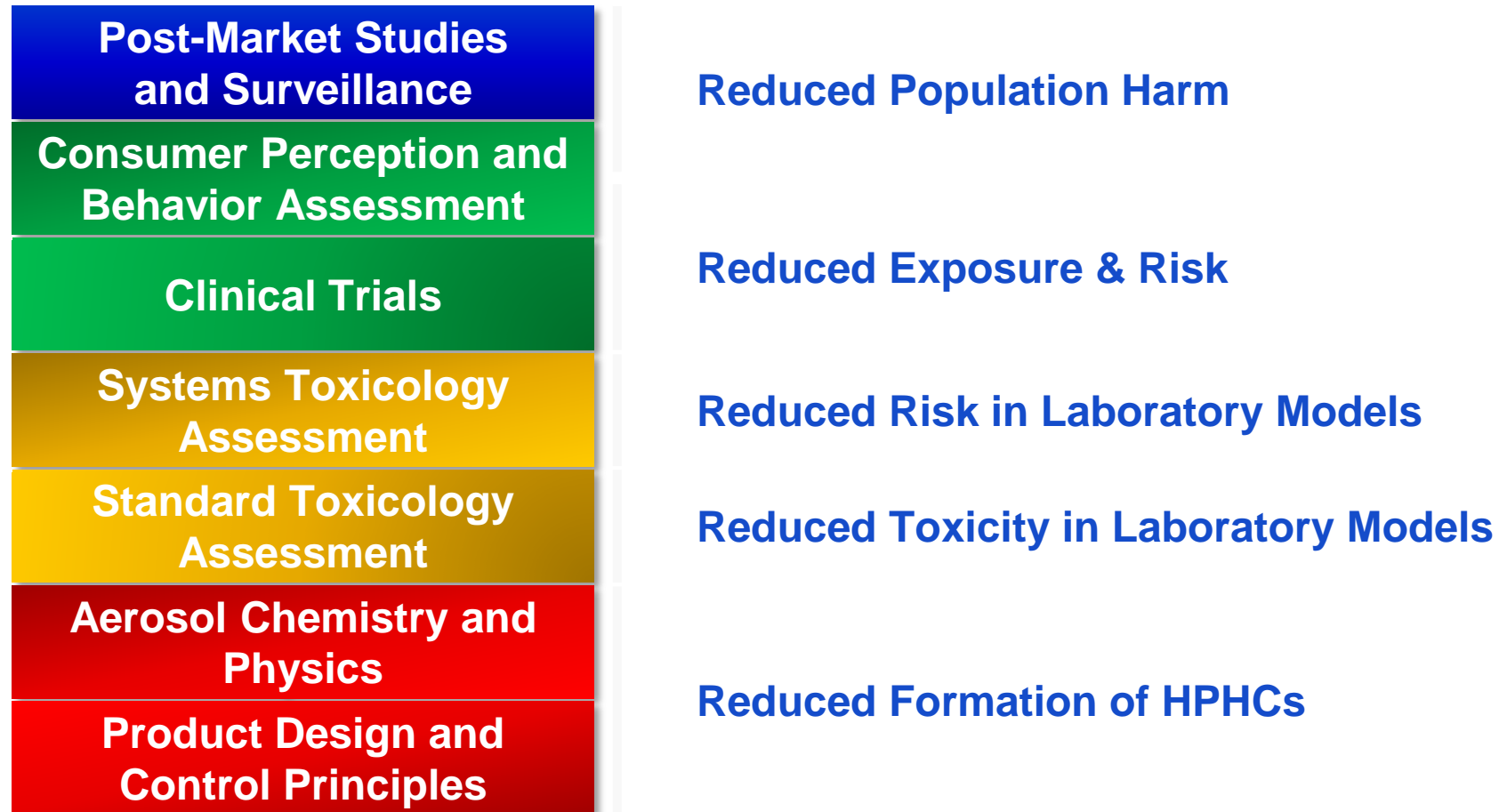
* <http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html>
Figure adapted from Clive Bates' presentation to E-Cigarette Summit (19 Nov 2013)

THS 2.2 Comparison with Continued Smoking and Cessation



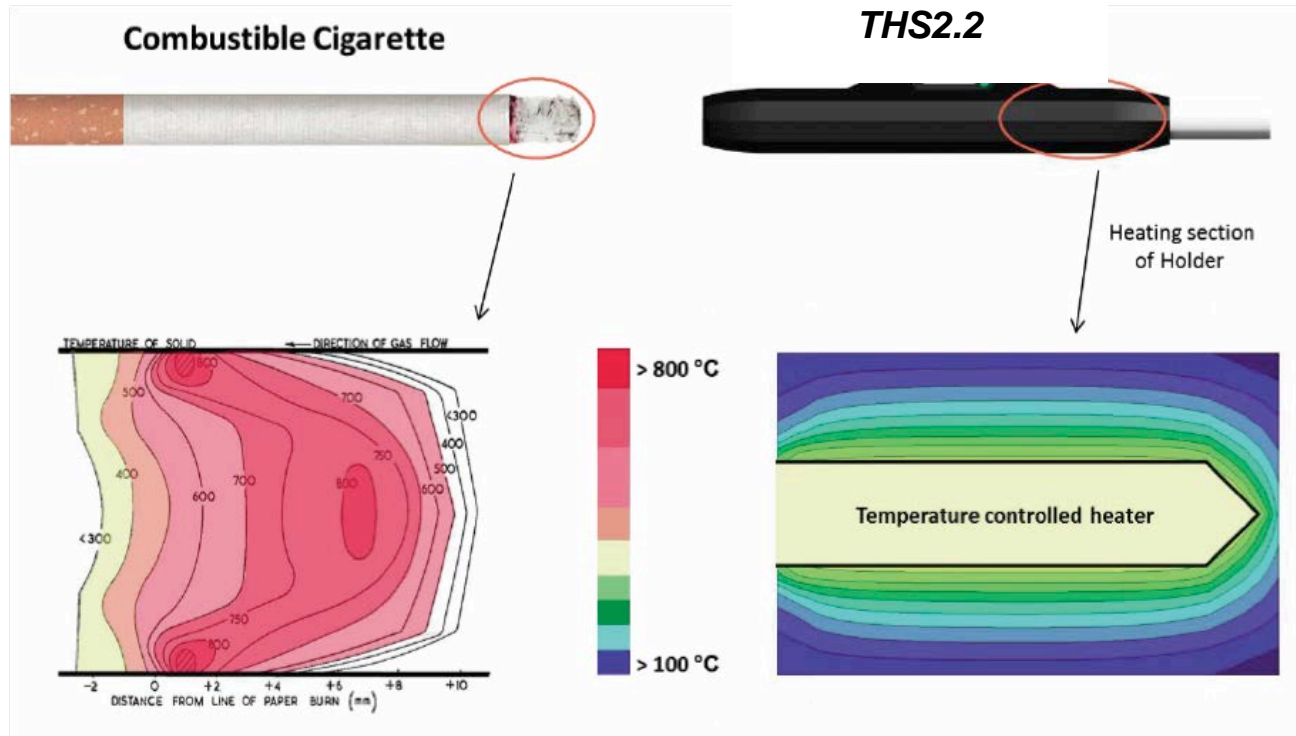
The U.S. Institute of Medicine (IOM), called **smoking cessation** the “*gold standard*” for the assessment of an RRP, providing “*an aspirational goal for risk and exposure.*”

Substantiating Reduced Risk: Totality of Scientific Evidence

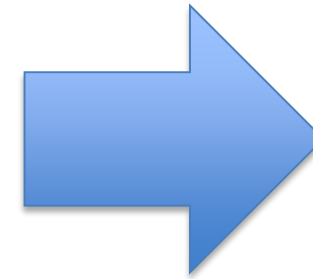


Source: Smith, M.R., *et al.*, Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program. *Regulatory Toxicology and Pharmacology* (2016). <http://dx.doi.org/10.1016/j.yrtph.2016.07.006>

Aerosol Chemistry: No Combustion, Reduced Formation



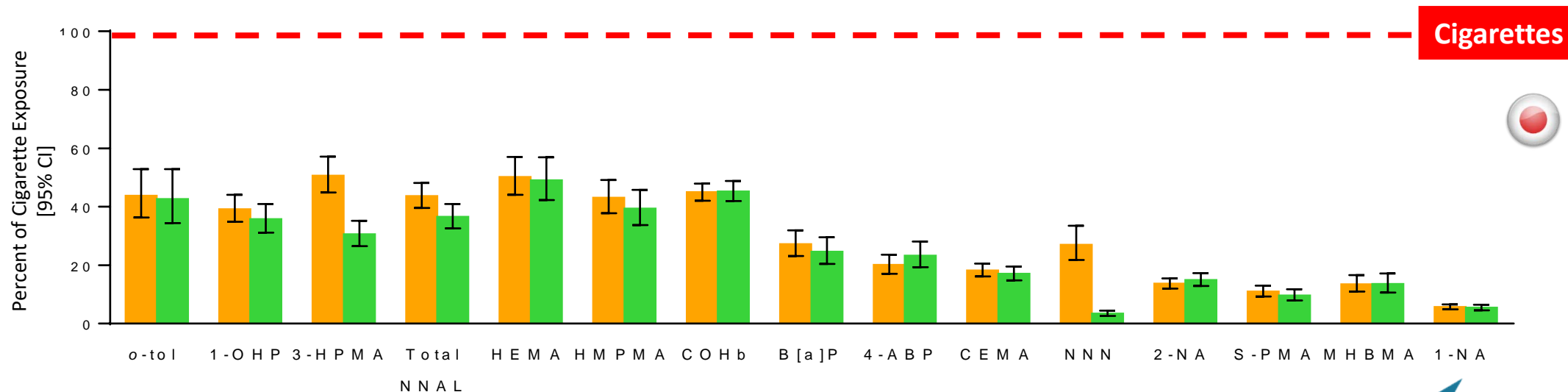
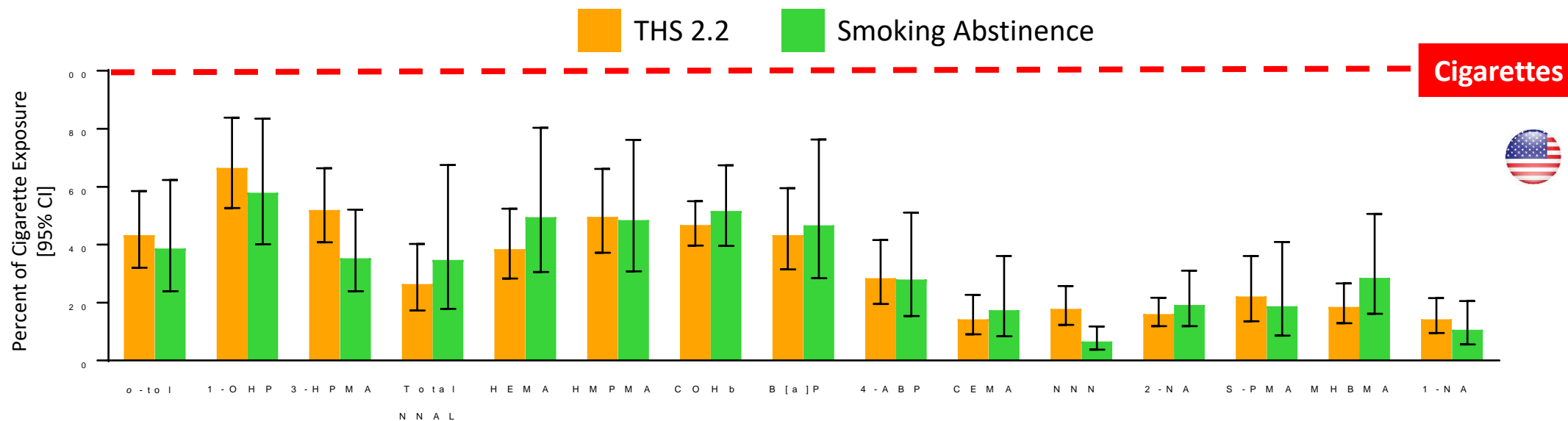
Cigarette smoke



THS 2.2 aerosol



Clinical Assessment: Reduced Exposure



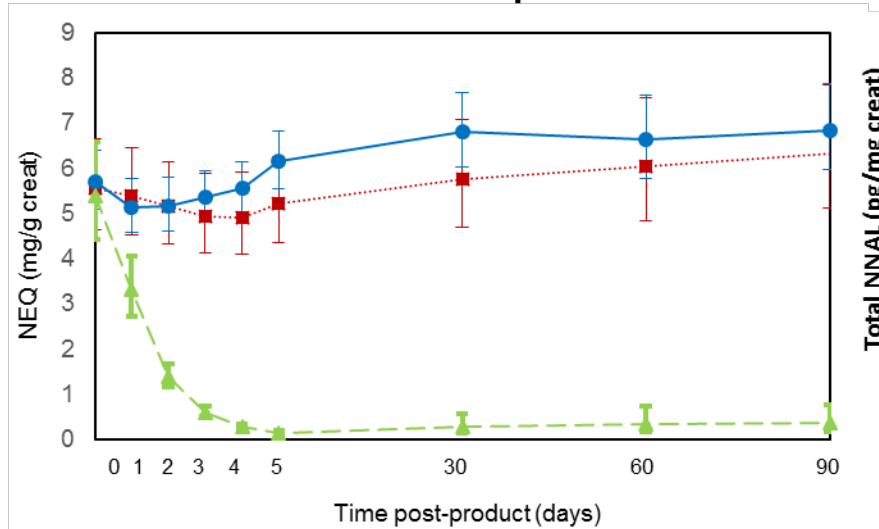
THS 2.2 : Exposure Reduction and Use over 90 Days in Japan

Adult smokers used the products ad libitum

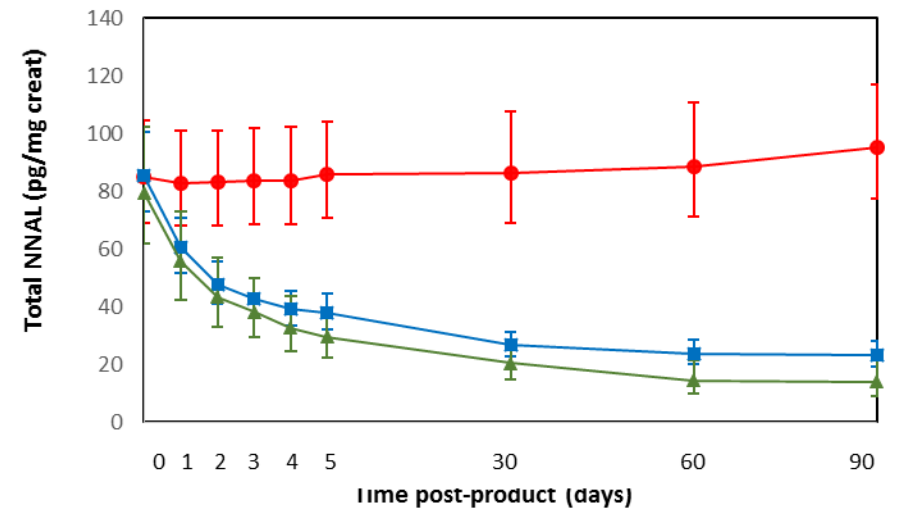
Adult smokers randomized to cigarettes or THS 2.2 were free to use the product as often as they wished in the clinic (five days) and then ambulatory (85 days)

—■— THS 2.2 —●— Combustible Cigarette —▲— Cessation

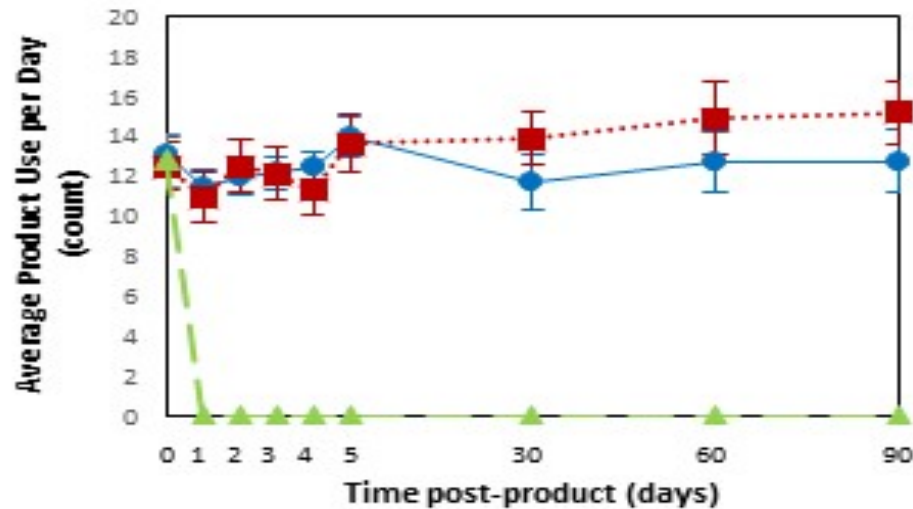
Nicotine Exposure



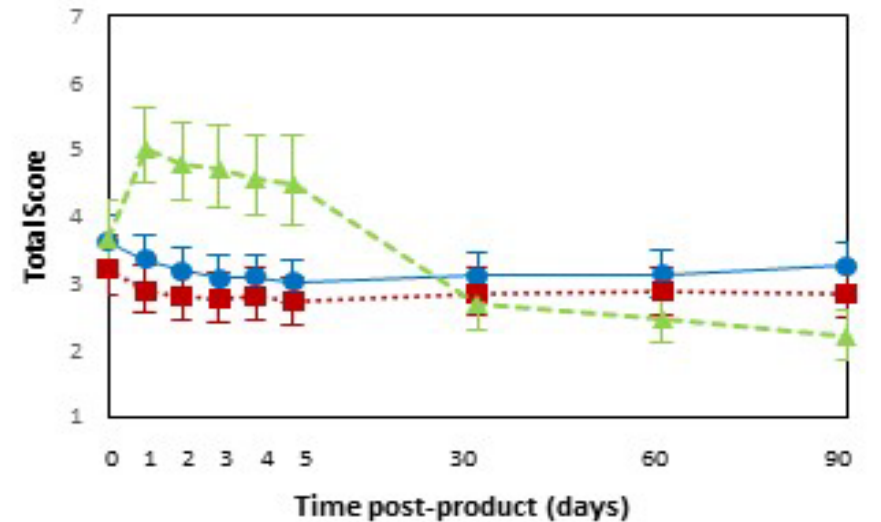
Total NNAL – Biomarker of NNK



Daily Product Use



QSU-brief



Clinical Changes after 90 Days

Reduced Exposure in Healthy Human Subjects



Disease Pathway	Endpoint	Abstinence Effect at 3m [95% CI]		Switching to THS2.2 Effect at 3m [95%CI]
Lipid Metabolism	HDL-C	0.0 mg/dL [-5.77; 5.84]	↑	1.4 mg/dL [-2.3;5.0]
Inflammation	WBC	-0.94 10 ⁹ /L [-2.00; 0.13]	-	0.17 10 ⁹ /L [-0.47; 0.81]
Airway Impairment	FEV1	2.0 % pred [-3.37; 7.36]	↑	0.53 % pred [-2.79; 3.85]
Endothelial Dysfunction	sICAM-1	-9.9 % [-19.7;1.1]	↓	-10.6 % [-16.7; -4.0]
Oxidative Stress	8-epi-PGF2 α	-8.5 % [-25.13; 11.8]	↓	-13.5 % [-23.6;-1.95]
Clotting	11-DTX-B2	-7.2 % [-37.7; 38.3]	↓	-3.6 % [-24.6; 23.3]



Disease Pathway	Endpoint	Abstinence Effect at 3m [95% CI]		Switching to THS2.2 Effect at 3m [95% CI]
Lipid Metabolism	HDL-C	6.4 mg/dL [2.5; 10.3]	↑	4.5 mg/dL [1.17, 7.88]
Inflammation	WBC	-0.41 10 ⁹ /L [-0.95; 0.14]	↓	-0.57 10 ⁹ /L [-1.04, -0.10]
Airway Impairment	FEV ₁	1.94 % pred [-0.44; 4.31]	↑	1.91 % pred [-0.14, 3.97]
Endothelial Dysfunction	sICAM-1	-10.9 % [-17.8; -3.4]	↓	-8.7 % [-14.94;-2.05]
Oxidative Stress	8-epi-PGF _{2α}	-5.9 % [-17.1; 6.8]	↓	-12.7 % [-21.81;-2.55]
Clotting	11-DTX-B ₂	-19.4 % [-30.1; -7.0]	↓	-8.98 % [-19.52, 2.94]

Long-Term Assessment (Post-Market)

1

Safety Surveillance

Measures:

Non-clinical data,
literature review, active
safety monitoring,
passive safety
surveillance

Call Center to Report
Health Event

2

Cross-Sectional Surveys

Measures:

Prevalence of use
Initiation/cessation
Use patterns

Point Prevalences Over
Time

3

Cohort Studies

Measures:

Characterization of THS
2.2 users
Real-world use data
Product perception
Biomarker of exposure &
effect

Risk, Behavior, Product Use

4

Population Health Impact Modeling

Measures:

Combines individual risk,
prevalence of use,
product use to estimate
population level harm

Dynamic Simulations Impact
of Product on Population

Clinical assessment of products aiming at reducing the risk of use compared with continued cigarette smoking

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Clinical Assessment: Clinical Studies

1

Pharmacokinetics/
pharmacodynamics

- Nicotine uptake
- Subjective effects

4 studies completed



2

Reduced exposure
1-week confinement

- Exposure to HPHCs
- Subjective effects
- Safety monitoring

2 studies completed



3

Reduced exposure
3-month ambulatory

- Safety monitoring

2 studies completed



4

Exposure response
6/12-month ambulatory
+ Smoking cessation
study

- Changes in clinical risk endpoints
- Safety monitoring

Ongoing

- Topline results for first 6 months expected by Q3 '17



- Additional 6 months by Q1 '18

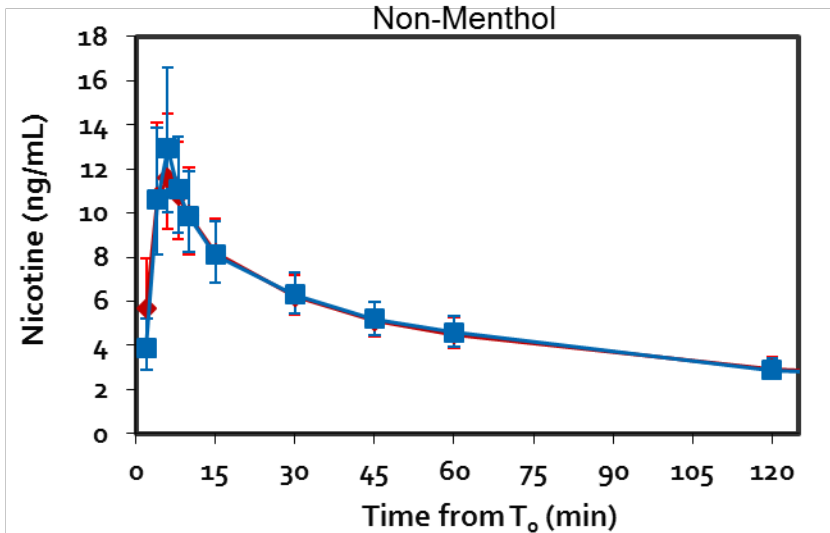


: Germany, Poland, and U.K.

PK Studies - Nicotine Exposure in Japan, U.S., and E.U.

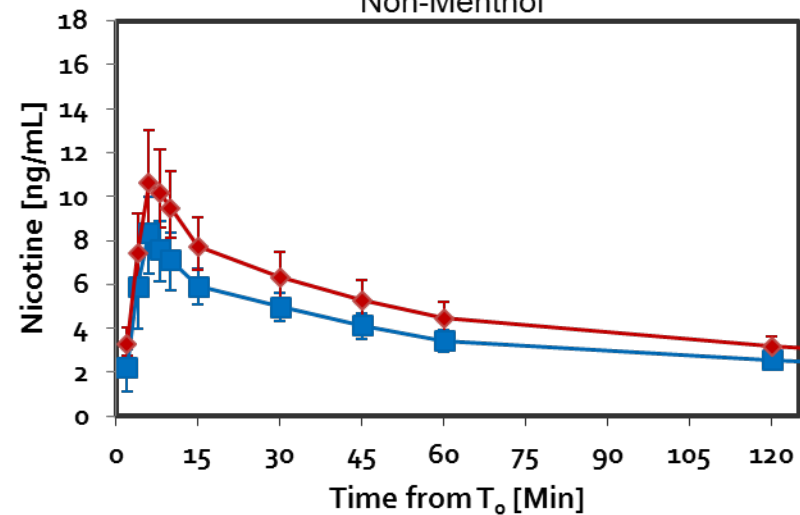
PK-02-JP

Non-Menthol



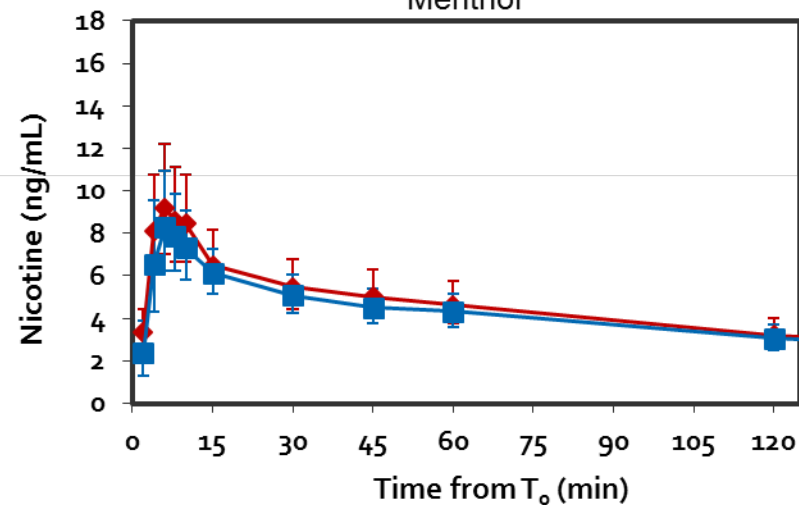
PK-01-EU

Non-Menthol



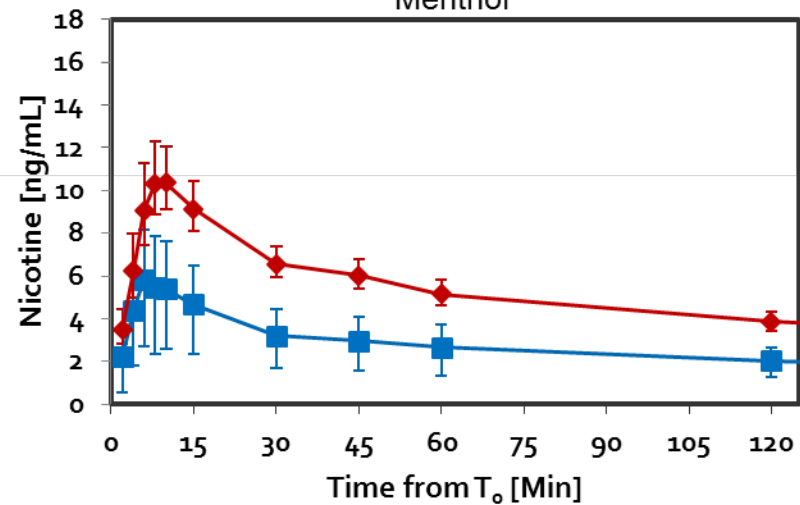
PK-05-JP

Menthol



PK-06-US

Menthol



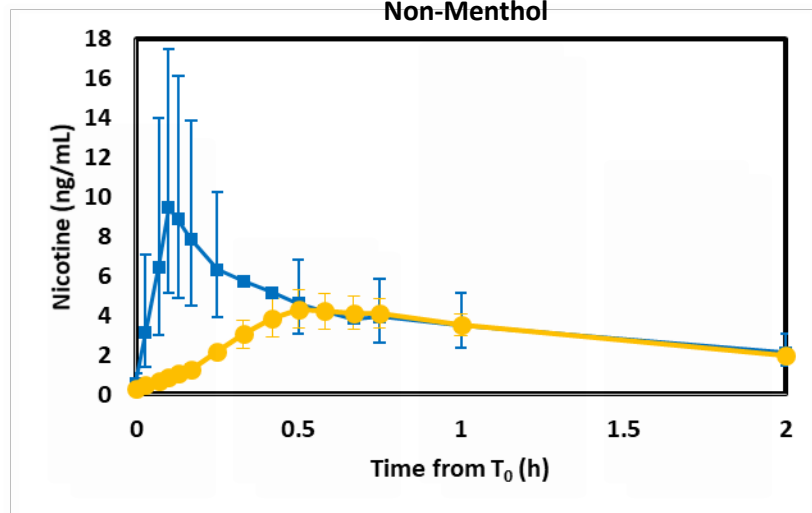
PK Studies - Nicotine Exposure in Japan, U.S., and E.U.

THS
2.2

NRT

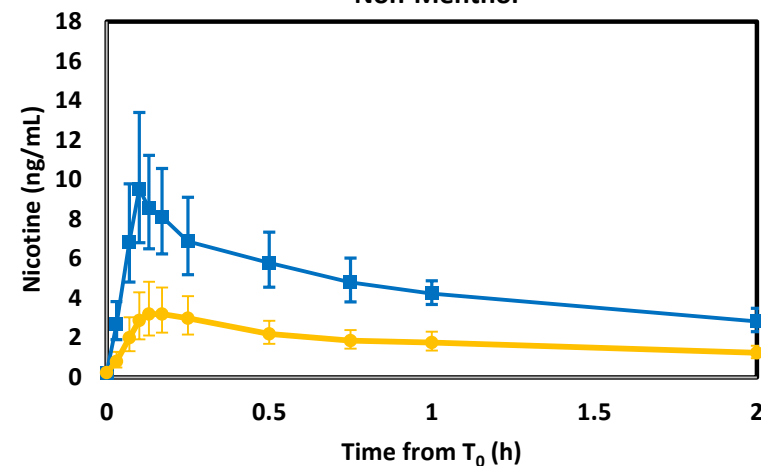
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Non-Menthol



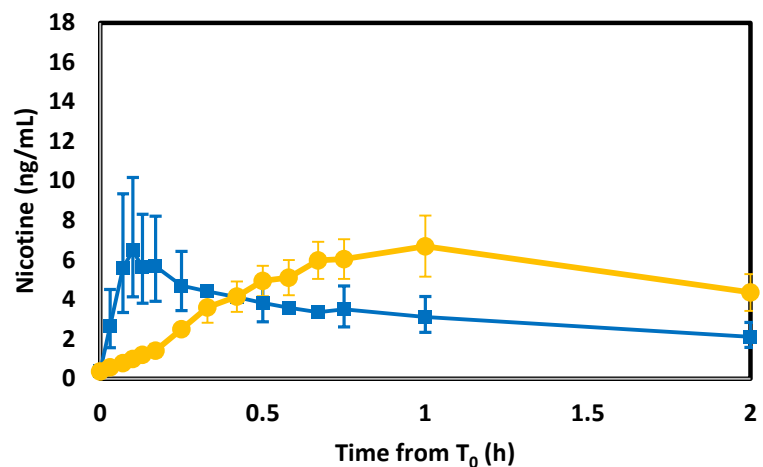
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Non-Menthol



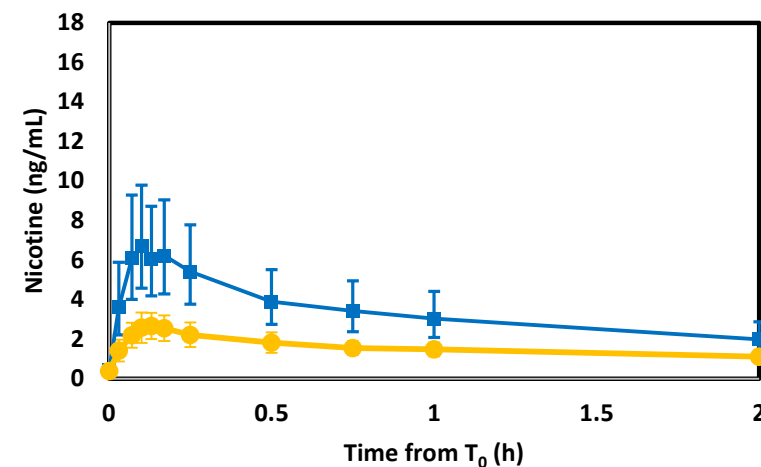
PK-05-JP

Menthol



PK-06-US

Menthol



Clinical Assessment: Clinical Evidence for Reduced Risk

Endpoint	Link to smoking-related disease		Expected direction of change for endpoint	Indication on direction of change in the Japan and U.S. 90-day studies
HDL-C	Cardio-vascular	Lipid metabolism	↑	✓ ✓
WBC		Inflammation	↓	✓
sICAM-1		Endothelial dysfunction	↓	✓ ✓
11-DTX-B ₂		Clotting	↓	✓ ✓
8-epi-PGF _{2α}		Oxidative stress	↓	✓ ✓
COHb		Acute effect	↓	✓
FEV ₁		COPD	Respiratory	↑
Total NNAL	Cancer	Genotoxicity	↓	✓ ✓

Perception & Behavior: Assessment

Perception and behavior assessment

1

Effect on tobacco use behavior among adult smokers

Assessing the likelihood that adult smokers:

- Will switch from cigarettes to THS
- Use THS in conjunction with cigarettes
- Switch back to cigarettes

Assessing the likelihood that adult smokers motivated to quit would instead switch to THS

2

Effect on tobacco use initiation among adult nonsmokers

Assessing the likelihood that adult never smokers and adult former smokers will initiate use of THS

3

Effect on consumer understanding and perceptions

Assessing the effect potential communications will have on:

- Enabling the public to comprehend information concerning modified risk claims
- Public perception about the health risks of using THS in comparison to ongoing smoking, NRTs, and cessation

Perception & Behavior: Summary of Results Collected to Date

- Summary of U.S. study results:
 - Less than 5% of adult former smokers and less than 1% of adult never smokers expressed an intention to use THS 2.2
 - Adult consumers correctly understood the modified risk communications, including that THS 2.2 is not without risk
 - A sizable proportion of adult smokers expressed an intention to use THS 2.2
- Post-market cross-sectional studies conducted in Japan and Italy confirmed that relapse and initiation were below 2% and 1%, respectively.

PMI is Committed to Transparency on RRP Science

- Leading RRP science
- State-of-the-art product assessment, with more than 1'400 patents granted
- Sharing and collaborating with the scientific community and regulators
- Approximately 200 peer-reviewed scientific publications since 2008, including: *American Journal of Physiology, Nature Biotechnology, Regulatory Toxicology, and Pharmacology Clinical studies registered ClinicalTrials.gov*
- Based on the principles of crowdsourcing and collaborative competition, the **sbv IMPROVER project** facilitates enhanced dialogue within the scientific community, transparency of research processes, and open innovation in scientific discovery
- A deeper review is warranted to obtain an independent assessment of several non-clinical and clinical studies: **SciPinion peer -review process** is a model for more in-depth insight and review by an independent panel of experts

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What are Reduced Risk Products? >

Watch our Overview Video

Our goals, our approach, our science.

Developing and Assessing less harmful alternatives to cigarettes.

FIND OUT MORE

Interactive Tour Discover the Cube

The case for Reduced Risk Products >

A message from President Reduced-Risk Products

Welcome Our Goals Our Approach Our Science

Sharing our RRP science

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Search for studies: Advanced

Find Studies About Clinical Studies Submit Studies Resources About This Site

Home > Find Studies > Search Results > Study Record Detail

Trial record 1 of 18 for philip morris products
Previous Study | Return to List | Next Study >

Nicotine Pharmacokinetic Profile and Safety of the Tobacco Heating System 2.2 (THS 2.2)

This study is currently recruiting participants.

Verified October 2013 by Philip Morris Products S.A.

Sponsor: Philip Morris Products S.A.

Information provided by (Responsible Party): Philip Morris Products S.A.

Checkoff Fields.gov Identifier: NCT01955607

First review: October 9, 2013
Last updated: October 9, 2013
Last verified: October 2013
History of Changes

nature biotechnology

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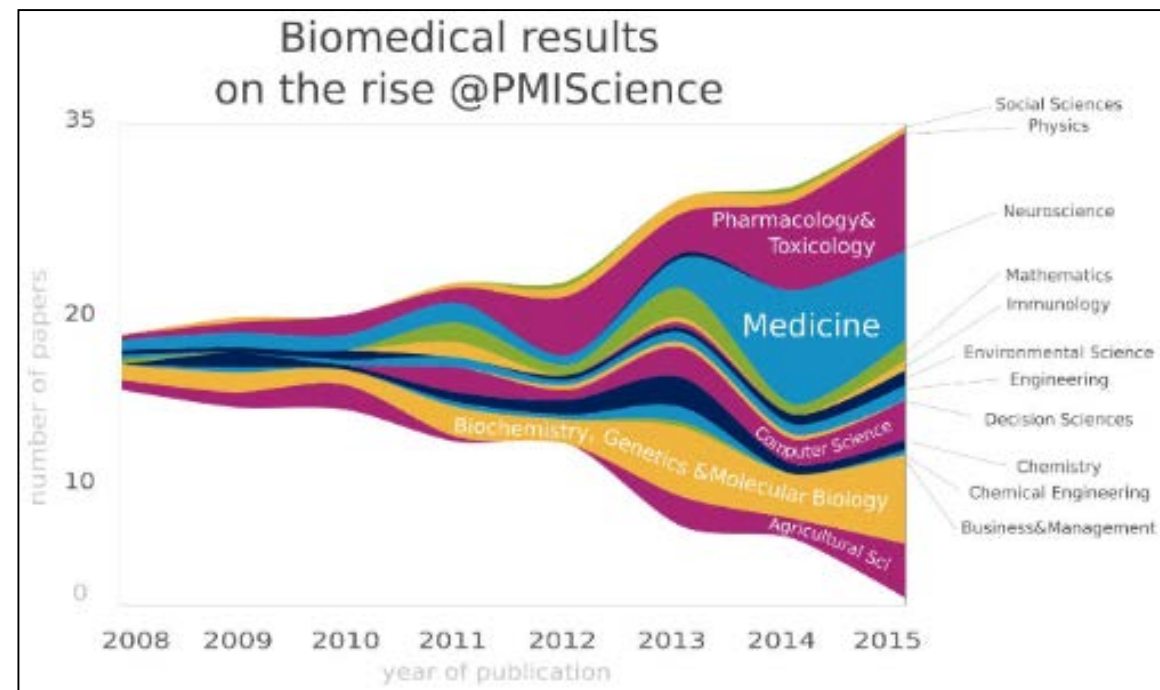
NATURE BIOTECHNOLOGY | COMPUTATIONAL BIOLOGY | COMMENTARY

Verification of systems biology research in the age of collaborative competition

Pablo Meyer, Leonidas G Alexopoulos, Thomas Bonk, Andrea Califano, Carolyn R Cho, Alberto de la Fuente, David de Graaf, Alexander J Hartemink, Julia Hoeng, Nikolai V Ivanov, Heinz Koepfli, Rune Linding, Daniel Marbach, Raquel Norel, Manuel C Peitsch, J Jeremy Rice, Ajay Royyuru, Frank Schacherer, Joerg Sprengel, Katrin Stolle, Dennis Vitkup & Gustavo Stolovitzky

Affiliations | Corresponding author

Nature Biotechnology 29, 811–815 (2011) | doi:10.1038/nbt.1968
Published online: 08 September 2011

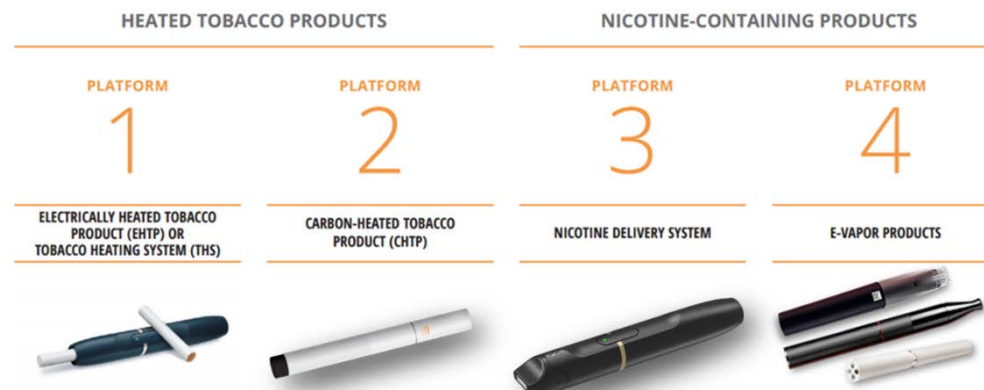


Summary – RRP's

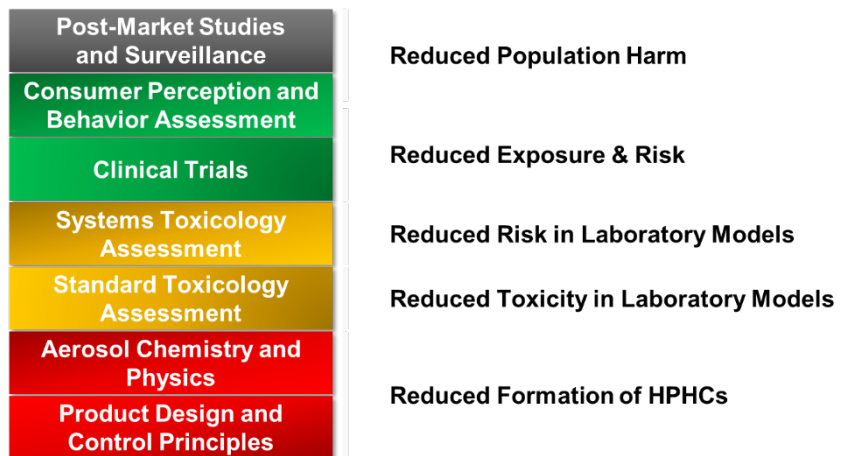
1



2



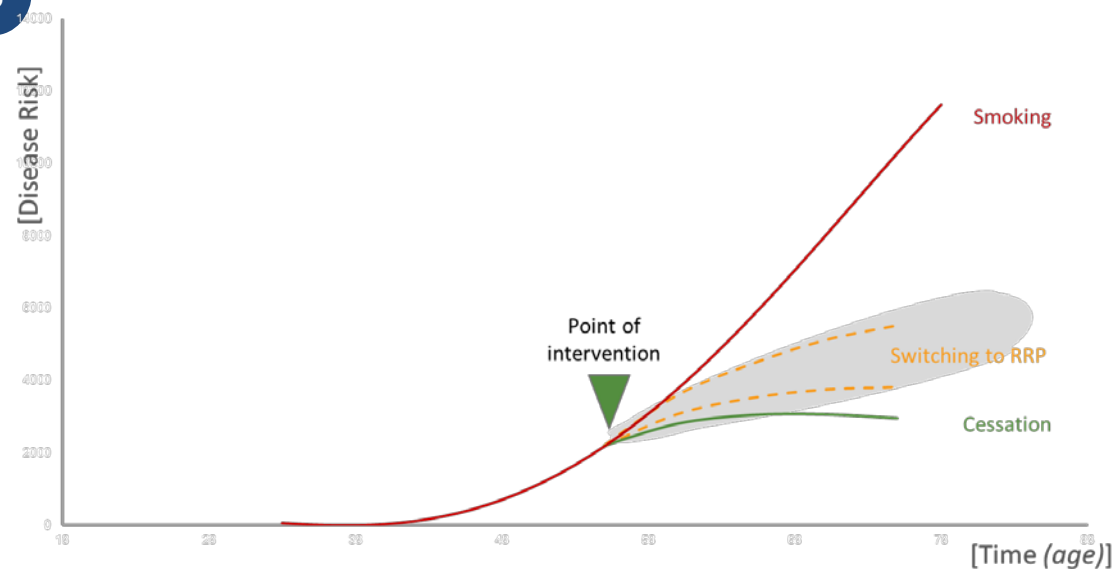
4



We are committed to **transparency** and encourage **independent verification** of our results.

www.PMIScience.com

3



The Objective is Harm Reduction



A screenshot of the Philip Morris International website. The header reads "Philip Morris International" in white text on a dark background. Below it, the main headline is "Designing a Smoke-Free Future" in large white font. Underneath the headline is the sub-headline "How long will the world's leading cigarette company be in the cigarette business?" and a "READ MORE" button with a right-pointing arrow. At the bottom of the page, there is a navigation bar with four blue buttons: "CONSUMER Corner" (with a person icon), "CAREERS at PMI" (with a paper plane icon), "INVESTOR Relations" (with a bar chart icon), and "MEDIA Center" (with a hashtag icon). A "SCROLL DOWN" button with a downward arrow is located in the bottom left corner of the page.

“Our stated ambition is to convince all current adult smokers that intend to continue smoking to switch to smoke-free products as soon as possible.”

André Calantzopoulos, CEO Philip Morris International