# HOLISTIC RISK REDUCTION IN RECALCITRANT SMOKERS

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Currently employed at Philip Morris International working on the scientific engagement team focused on harm reduction and our smoke-free products



# The Burden of Non-Communicable Diseases (NCD)





Source: <a href="https://www.who.int/nmh/countries/phl\_en.pdf?ua=1">https://www.who.int/gho/ncd/mortality\_morbidity/en/</a> (Accessed: February 2021)

### **CVD Mortality Trends: Developed Countries**

**Figure** 69 Trends in CVD mortality rates (age standardized) in developed countries (*xi*).



Source: <u>https://www.world-heart-federation.org/wp-content/uploads/2017/05/Global\_CVD\_Atlas-min-1.pdf</u> (Accessed: February 2021)

### **Risk Factors for Cardiovascular Disease Mortality — the Philippines**



Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization 2019. University of Washington (2021). http://ihmeuw.org/5d8x (Accessed: February 2021)

# **Strategies to Reduce the Number of Smokers**



#### Initiation / Re-Initiation Prevent Non-Smokers Starting Including never & former smokers

**Cessation** Maximize Smokers Quitting Tobacco and nicotine altogether **Harm Reduction** 

Making less harmful alternatives available for smokers who would otherwise continue to smoke



# Smoking Cessation in the US: 2000-2015



■ Interested in quitting ■ Made past-year quit attempt ■ Recent cessation



Source: Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting Smoking Among Adults — United States, 2000–2015. MMWR Morb Mortal Wkly Rep 2017;65:1457–1464.

# Unsupported Quitting – "Cold Turkey"



3-5%

### Achieve smoking abstinence for 6-12 months



Source: https://www.fda.gov/consumers/consumer-updates/fact-or-fiction-what-know-about-smoking-cessation-and-medications (Accessed; February 2021) Hughes et al. 2004 Addiction. 2004 Jan;99(1):29-38 (doi: 10.1111/j.1360-0443.2004.00540.x)

# **Cessation with Medication – Long-Term Quit Rates**



Nicotine patch, gum, lozenge, inhaler, nasal spray

Non-Nicotine Treatments



## **Despite This...Smoking Prevalence Remains High**

- Globally, >1 billion people will continue to smoke through to 2025<sup>1</sup>
- Many smokers continue to smoke, even after CVD diagnosis

# **49%** Coronary artery disease (CAD):

... of those who smoke at the time of event, smoked 6 months later  $^2$ 

#### Stroke:

... of stroke survivors who smoked were smoking 3 months afterwards <sup>3</sup>

## 72% Pe

57%

#### Peripheral artery disease (PAD):

... of smokers with new/worsening claudication were smoking 12 months later <sup>4</sup>

- 1. <u>WHO Global Report on Trends in Prevalence of Tobacco Use 2000-2025</u>, 3rd edition (December 2019)
- 2. Kotseva 2016 (Eur J Prev Cardiol 2016 Apr;23(6):636-48)
- 3. Sauerbeck 2005 (J Neurosci Nurs 2005 Dec;37(6):316-9, 325)
- 4. Patel 2018 (J Am Heart Assoc 2018 Oct 16;7(20):e010076. doi: 10.1161/JAHA.118.010076)



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#### What Is the Objective of Harm Reduction?

#### **Unhealthy Behaviors**

Accept that some level of unhealthy behavior is inevitable.



#### **Minimize Harm**

Harm reduction targets to minimize the harms resulting from unhealthy behaviors

#### People make poor lifestyle choices despite suffering negative health effects

- Ischemic heart disease (IHD) patients  $\rightarrow$  continue to lead sedentary lives & practice an unhealthy diet
- Diabetic patients  $\rightarrow$  continue to overeat and eat unhealthy foods
- Chronic obstructive pulmonary disease patients  $\rightarrow$  continue to smoke

#### Harm reduction is successfully applied in many areas.



\* http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html (Accessed: February 2021)

#### Harm Reduction — At the Population Level





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







- > 6,000 chemicals identified in cigarette smoke
- Almost 100 of them are know to cause disease (Harmful or potentially harmful constituents "HPHCs")





Source: Baker R. R., 1975, Temperature variation within a cigarette combustion coal during the smoking cycle, High Temp. Sci., 7, 236-247. Coloration by PMI.

# As the temperature increases $\rightarrow$ the emission of HPHCs increases



Source: McGrath et al. 2007, Food and Chemical Toxicology 45,6,1039-1050



# What happens if you can eliminate combustion?



# Absence of Combustion

#### 400 350 Temperature / (°C) 007 120 120 120 120 10 50 50 100 150 200 250 300 350 Time / (s)

Heating Tobacco

Maximum temperature far below the temperature tobacco ignites

Tobacco temperature decreases when air is drawn into the tobacco heating system

Without the heating source the tobacco temperature decreases rapidly

The tobacco heating system is independent of oxygen









Source: April 26, 2018 Amendment: Submission of P1 Characterization Study Available @ www.fda.gov accessed on February 3, 2021

*in vitro* Assessment







#### **Clinical Assessment - Reduced Exposure Studies**









Source: Haziza et al. (2019) Nicotine Tob Res 2020 Apr 17;22(4):539-548. doi: 10.1093/ntr/ntz013. COHb: Carboxyhemoglobin; 3-HPMA: 3-hydroxypropyl mercapturic acid

THS

# Reduced Exposure Studies

In Healthy Smokers Switching Compared to Continued Smoking

THS Smoking abstinence



# Switching completely to THS helps achieve almost 95% of the reduction in exposure that is achieved by smoking abstinence.







Switching = 2 months of Cigarette Smoke exposure followed by 6 months of either THS (= THS Switch) or Fresh Air (= Cessation) Source: Phillips et al. Toxicol Sci. 2016 Jun;151(2):462-4. doi: 10.1093/toxsci/kfw062.

# **Clinical Assessment** 6 Month Exposure Response Study + 6 Month Extension Study

- Epidemiologic link to smoking-related disease?
- Affected by smoking status
- Reversible upon smoking cessation

Assess the changes across a set of "8 coprimary clinical risk endpoints "(CRE) in smokers who switch from smoking cigarettes to using THS relative to those in smokers who continue to smoke cigarettes for 6 months

# Coprimary endpoints representative of pathomechanisms

Lipid metabolism	HDL-C
Clotting	11-DTX-B2
Endothelial function	sICAM-1
Oxygen Delivery	COHb
Inflammation	WBC
Oxidative stress	8-epi-PGF <sub>2α</sub>
Lung function	FEV <sub>1</sub>
Genotoxicity	Total NNAL



Note: THS stands for Tobacco Heating System Registered on clinicaltrials.gov: NCT026396381; Results submitted to the U.S. FDA on June 8, 2018, as an amendment to PMI's MRTP Application for THS



Source: A 26-week Extension of the ZRHR-ERS-09-US Study Evaluating Biological and Functional Changes in Healthy Smokers After Switching to THS (ClinicalTrials.gov: NCT02649556)

### **Do Smokers Switch to Less Harmful Products?**



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Source: National Health and Nutrition Survey, Japan (2020)

### Study Results — Heated Tobacco Product Survey (2019)

#### Smoking status at time of starting Heated Tobacco Product use (%)



# Study Results — General Population Survey (2019)

Initiation<sup>\*</sup> with tobacco and nicotine-containing products



PMI cross-sectional surveys

\* Initiation within the last 12 months prior to the survey in adult never-users of tobacco and nicotine-containing products. Source: P1-PMX-01-JP; P1-PMX-02-IT; P1-PMX-03-DE

### Independent Study Results in Youth

#### Kuwabara et al. (2020)

- •2017 lifestyle survey in adolescents
- Population:
  - •98 of 10,325 junior high schools (age group, 12–15 years)
  - •86 of 4,907 high schools (age group, 15–18 years) randomly selected
- •Sample size: 64,152 (age group, 12–18 years)
- •Survey dates:
  - Data collection between December 2017 and February 2018



	Cigarettes			Heated tobacco*			E-cigarettes		
Use	Ever	Monthly	Daily	Ever	Monthly	Daily	Ever	Monthly	Daily
Junior high school	2.6%	0.6%	0.1%	1.1%	0.5%	0.1%	2.1%	0.7%	0.1%
High school	5.1%	1.5%	0.5%	2.2%	0.9%	0.1%	3.5%	1.0%	0.1%

\*Includes a number of different Heated Tobacco Products



### US FDA's Review of the Scientific Evidence on THS

#### Absence of Combustion

The low temperature in the system (≤350°C), the lack of an exothermic process, the similar levels of HPHCs in the presence and absence of oxygen, and the low level of nitrogen oxides in the aerosol ... suggest that combustion does not occur

#### • Reduced Emissions

Compared with combustion in cigarettes, the process used to heat tobacco ... significantly reduces the production of harmful and potentially harmful chemicals

• Reduced Toxicity

The non-clinical evidence suggests a lower toxic potential

Reduced Exposure

The magnitude of difference in biomarkers of exposure (BOEs) observed when smokers switch completely is substantial

#### • Likely Substantial Reduction in Morbidity or Mortality

Although reduced risk has not been demonstrated, the totality of evidence presented suggests that a measurable and **substantial reduction in morbidity or mortality** among individual tobacco users is reasonably likely in subsequent studies

#### • Consumers Perception & Behavior

**Consumer understanding is in line with the relative risks** of the product that are reasonably likely based on the current state of the evidence



Source: https://www.fda.gov/media/139796/download (modified to remove branding)

#### **Overall FDA Conclusions**

The applicant has demonstrated that the products sold or distributed with the proposed modified risk information meet the standard under section 911(g)(2) of the FD&C Act, including that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies, and issuance of an order is expected to 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.



#### Conclusions

The best option for any smoker is to quit smoking altogether

Quitting is hard, and although many smokers try to quit, most do not. Majority of smokers diagnosed with CVD do not quit smoking

A holistic approach is needed to truly help move smokers away from cigarettes

Scientific evidence and monitoring is required, but harm reduction can complement existing tobacco control

