PHILIP MORRIS

AUSTRALIA NEW ZEALAND PACIFIC ISLANDS

Briefing Note: Tobacco Harm Reduction

27 February 2018

In Australia, only smoking is permitted

Philip Morris International (PMI) has publicly announced a global commitment to a Smoke-Free Future. In Australia, this commitment is unachievable due to Commonwealth laws banning the sale of low risk alternatives to cigarettes (which we refer to as Reduced Risk Products or RRP), such as electronic vaporisers. Only "tobacco products prepared and packed for smoking" are allowed.

Australian smoking prevalence rates have stagnated

The most recent **Australian Department of Health** report[1] on smoking rates in Australia states:

- that for the first time in more than 2 decades, the daily smoking rate did not significantly decline over the most recent 3-year period; and
- there was only a slight and non-significant decline in the number of cigarettes smoked per week

The opportunity

Professor Ron Borland, the Nigel Gray Distinguished Fellow in Cancer Prevention at Cancer Council Victoria co-authored a series of papers estimating the population health impact of RRPs, developing *A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products* in 2016. Last year, the same lead authors published a study[2] based on this population health impact framework which found that in the United States:

> *"Compared with the Status Quo, replacement of cigarette by e-cigarette use over a 10-year period yields 6.6 million fewer premature deaths with 86.7 million fewer life years lost in the Optimistic Scenario. Under the Pessimistic Scenario, 1.6 million premature deaths are averted with 20.8 million fewer life years lost. The largest gains are among younger cohorts, with a 0.5 gain in average life expectancy projected for the age 15 years cohort in 2016."*

In Australia this would equate to preventing about 500,000 smoking-related deaths.

International best practice

Earlier this month, **Public Health England** released an evidence review[3], the main findings include:

- vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits
- e-cigarettes could be contributing to at least 20,000 successful new quits per year and possibly many more
- e-cigarette use is associated with improved quit success rates over the last year and an accelerated drop in smoking rates across the country
- many thousands of smokers incorrectly believe that vaping is as harmful as smoking; around 40% of smokers have not even tried an e-cigarette
- the evidence does not support the concern that e-cigarettes are a route into smoking among young people (youth smoking rates in the UK continue to decline, regular use is rare and is almost entirely confined to those who have smoked)

[1] Australian Institute of Health and Welfare, *National Drug Strategy Household Survey 2016: detailed findings* (available here).
[2] Levy et al. Tobacco Control Journal, *Potential deaths averted in USA by replacing cigarettes with e-cigarettes* (available here).
[3] Public Health England, *E-cigarettes and heated tobacco products: evidence review* (available here).

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In July 2017, the UK Department of Health and Social Care published a 5 year national tobacco strategy, *Towards a smoke-free generation: tobacco control plan for England*, as one of the UK's national ambitions a commitment to:

- Help people to quit smoking by permitting innovative technologies that minimise the risk of harm
- Maximise the availability of safer alternatives to smoking

The **United States Food and Drug Administration** is also looking to innovative technologies and strategies to reduce smoking, last year releasing a Comprehensive Approach to Nicotine and Tobacco (summarised in the attachment).

The United States Congress has established the Centre for Tobacco Products within the FDA to regulate the manufacturing, marketing, and distribution of tobacco products. FDA can also issue an order authorising the marketing of a modified risk tobacco product (MRTP), but only if the evidence submitted in the application meets the requirements of the relevant legislation. For example, an MRTP application musts demonstrate that the product will or is expected to benefit the health of the population as a whole.

What has PMI done?

PMI has submitted an MRTP application to the US FDA for IQOS, one of our RRPs. We expect our evidence to be reviewed in the coming months. Outside of the United States, our efforts to convert those smokers who can't or won't quit have resulted in:

- **Nearly 5 million** adult smokers around the world have already stopped smoking and switched to *IQOS*, with approximately **10,000 smokers switching** every day.
- **Over USD 4.5 billion** invested to develop and substantiate the reduced-risk profile of, and build manufacturing capacity for a wide portfolio of smoke-free products since we became a public company in 2008.
- *IQOS* is present in key cities or nationwide in **38 markets**, including developed and developing countries. Our priority in 2018 is to go deeper with *IQOS* into existing launch markets.
- We are transforming our business away from cigarettes, with **almost 13% of our total net revenues** were already represented by smoke-free products in 2017, growing from $64 million in 2015 to $3.6 billion in 2017.

These figures demonstrate our commitment to smoke-free products, which will play a pivotal role for more than one billion people who smoke globally and can therefore make a significant contribution to public health. Australia's ban on all products except cigarettes negatively impacts public health and denies the opportunity to change the lives and health trajectories of millions of Australian smokers.

Outcomes sought

1.	**Evidence based policy on harm reduction in Australia:** Tobacco harm reduction approaches that successfully reduce smoking rates internationally should be investigated and discussed in Australia. Australia has missed all of its targets under the current National Tobacco Strategy and Tobacco Harm Reduction should be central to the next one.
2.	**Undertake a population health impact study:** Study the population health impact of RRPs, taking into account all positive and negative health consequences, to establish the overall range of public health benefit / detriment. International assessments of the worst case scenario repeatedly demonstrate a significant public health opportunity.
3.	**Establish a regulatory scheme to review evidence and approve RRP applications**: Create a regulatory regime for RRPs, as the United States, European Union and the United Kingdom have done, and as New Zealand and Canada have announced they will do.

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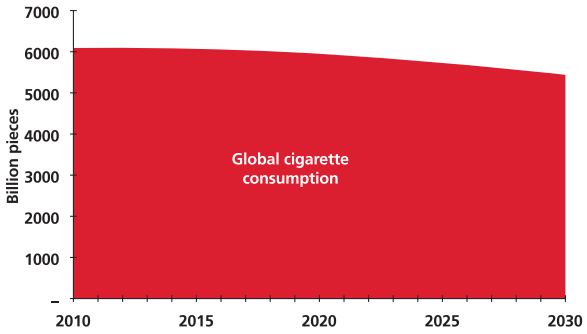
The Problem

Cigarette smoking is one of the leading preventable causes of death and illness in the world.

The best way for people to eliminate the adverse health consequences of smoking is to never start, and, for smokers, to stop. However, many smokers either do not want to quit or find it very difficult to quit, and thus continue to consume a dangerous product.

An approach for these smokers is the development of non-combustible products that are proven to be less harmful and are acceptable alternatives to cigarettes.

Cigarette global consumption trend projection to 2030



Consumption 2010–2030 on parabolic trend projection from 1908–2012 data from Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. JAMA 2014; 311: 183–92.

In addition to projections by public health experts showing limited declines in cigarette consumption, the World Health Organization's projections of worldwide smoking prevalence, when combined with population growth projections, show that there will be more than one billion smokers for the foreseeable future despite declining smoking prevalence. Based on these projections, the expected toll of smoking-related disease will remain constant.

National data show similar trends: even in countries with declining prevalence, the number of smokers is likely to remain flat or increase due to population trends, leading tobacco control experts to conclude that many tobacco control policies have reached either a limit on what can be done, or at least a state of greatly diminishing marginal returns.

So the question is…

Can reduced-risk tobacco products help those who continue smoking?

The results so far are promising and show that:

The levels of harmful and potentially harmful constituents in the aerosol of *IQOS*,[1] PMI's flagship reduced-risk product, are reduced by more than 90% on average compared to smoke from a standard research cigarette

Premarket research and post-market data show very little interest in *IQOS* among adult nonsmokers and former smokers with substantial potential for full switching among current adult smokers

Exposure to harmful and potentially harmful constituents measured in smokers who switched to *IQOS* approached the effect observed in smokers who quit smoking for the duration of clinical studies

To date, more than 3.7 million adult smokers worldwide have quit smoking and switched to *IQOS*. In six countries where *IQOS* is sold, 70% or more of *IQOS* purchasers predominantly or fully switch from cigarettes to *IQOS*. In several countries, that number approaches 80%.

1. *IQOS* is one of several products in Philip Morris International's portfolio of Reduced-Risk Products ("RRPs"). 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.

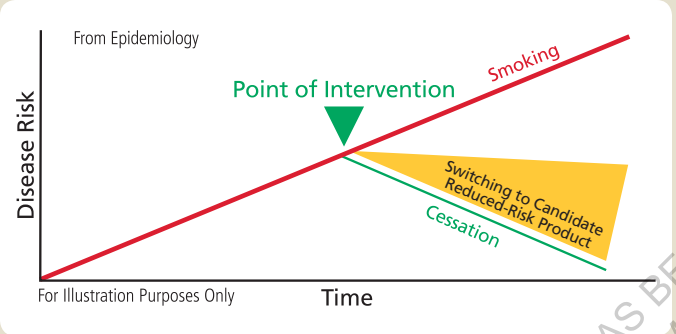
The Challenge

It is one thing to make a tobacco product that is less hazardous; it is quite another to do so while making the product acceptable and appealing so that adult smokers will want to switch to it from cigarettes. Less harm without appeal will generate little in the way of public health benefits. These are big challenges but ones, which, if met, can produce significant benefits for public health.

Reduced-Risk Product X **Product Acceptance and Usage** = **HARM REDUCTION**

Reduced risk tobacco products must also be marketed in a manner that conveys their benefits to adult smokers without encouraging never smokers, former smokers and especially youth to begin using them.

Philip Morris International's comprehensive assessment program is designed to address these challenges and follows relevant scientific precedents. Clinical and scientific assessment methods are similar to those used by the pharmaceutical industry, including product design controls, a range of toxicological tests, clinical studies, premarket consumer perception and behavior studies and post-market assessments.



The Goal: A Risk Profile Approaching Cessation

Philip Morris International's goal is to demonstrate that switching fully to its potentially reduced-risk products has a risk reduction profile approaching that of cessation, referred to by the United States Institute of Medicine (IOM) as the "gold standard" for assessing risk reduction.

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

Philip Morris International's Assessment of Reduced Risk Tobacco Products

The first step in assessing the aerosol generated by a reduced-risk product is to confirm a reduction in the levels of harmful and potentially harmful constituents (HPHCs) compared to cigarette smoke. HPHCs are considered to be the primary cause of smoking related diseases.

The next step is to confirm that the reduction in HPHCs results in reduced toxicity. Philip Morris International (PMI) takes toxicological assessment one step further using a new area of science known as systems toxicology which allows the use of non-clinical data to quantify the reduced impact of its products on the mechanisms leading to disease and thereby model their risk reduction potential compared with cigarettes.

Clinical studies are a cornerstone of the assessment program. They assess whether a reduction in the formation of HPHCs measured in the laboratory leads to a reduction in HPHC exposure under real use conditions when an adult smoker switches to the product; and they demonstrate whether switching from cigarettes to a reduced-risk product has a beneficial effect on a smoker's health profile. Clinical studies also help determine the extent to which adult smokers would find the product an acceptable alternative to cigarettes.

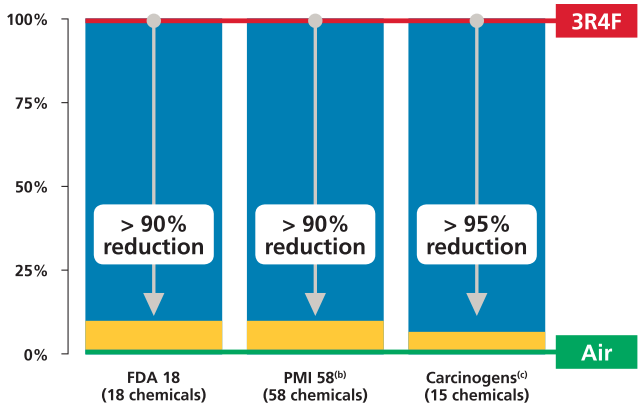
Premarket perception and behavior research is conducted to determine consumer understanding of the product's attributes and communications (including risk perception) and the extent to which marketing of the reduced-risk product will encourage adult smokers to switch as well as the likely impact on non-smokers and former smokers initiating tobacco use.

PMI's assessment of reduced-risk products continues after its products are placed on the market. Post-market studies are important to verify how consumers use the product, longer term risk and the product's impact on health of the population as a whole.

Philip Morris International's studies on *IQOS*, a heat-not-burn tobacco product, are well-advanced.

IQOS: Results Summary

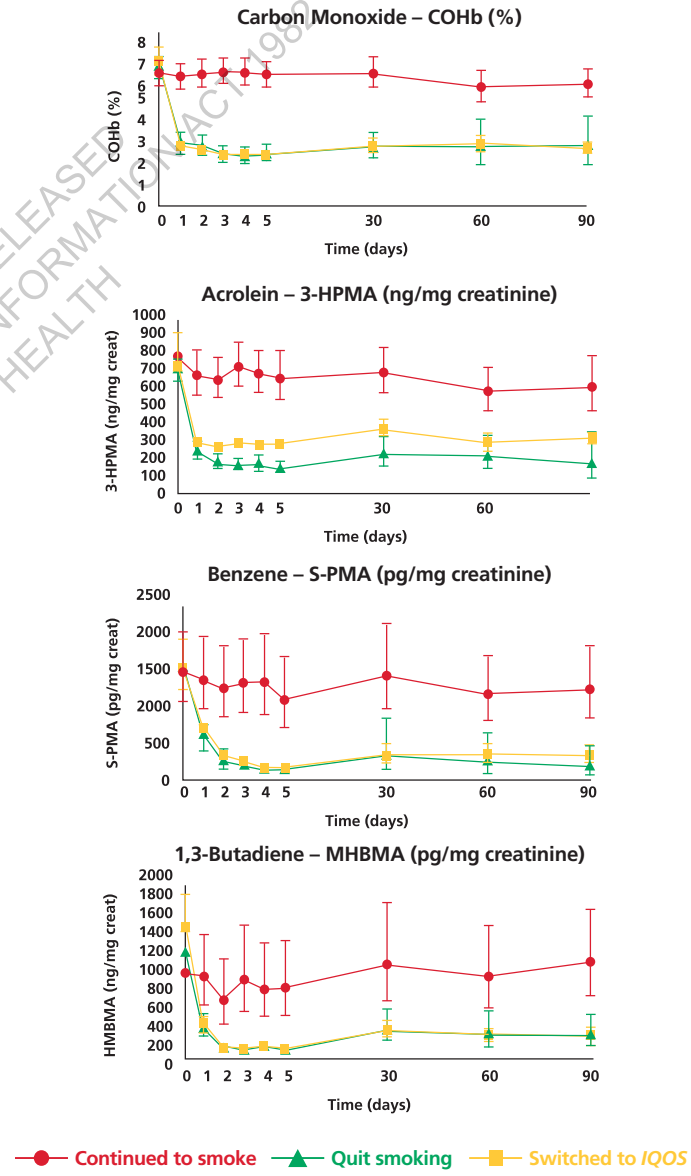
- The levels of chemicals classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens are reduced on average by more than 95% compared to a standard research cigarette (3R4F).[2] Similar reductions are found among the HPHCs designated by the U.S. Food and Drug Administration and among the 58 chemicals monitored by PMI.



- These reductions in the formation of HPHCs translate into significantly reduced toxicity compared to cigarette smoke as demonstrated in well recognized *in vitro* and *in vivo* tests and significantly reduced impact on disease mechanisms and disease progression relative to cigarette smoke as modeled through innovative systems toxicology assessments.

- The real life results in countries where *IQOS* is being sold are encouraging. In Italy and Romania, 78% of *IQOS* purchasers have fully or predominantly switched to it. In Portugal, a full or predominant conversion rate of 79% was achieved among *IQOS* purchasers. The conversion rate in Japan is even higher at 80%. PMI estimates that more than 3.7 million adult smokers worldwide have quit smoking and switched to *IQOS*.
- Premarket assessments show negligible interest in *IQOS* among adult never smokers and former smokers and substantial potential for full switching among adult smokers. In one study conducted in the United States. 0% of never smokers aged 18-25 said they intended to use *IQOS*, while up to 39% of adult smokers stated a high intention to use the product.
- At the same time, post-market cross-sectional population studies conducted in Japan, where *IQOS* commercialization is most advanced, show that nearly all *IQOS* users surveyed (more than 98%) smoked cigarettes or some other form of tobacco or nicotine-containing product before they used *IQOS*, 1.9% of all *IQOS* users started using tobacco products with *IQOS*, and 1.9% of those who had quit smoking cigarettes and later relapsed did so with *IQOS*. The overwhelming majority who relapsed went back to cigarettes.

- Three-month clinical trials recently carried out in the United States and Japan showed that smokers who switched to *IQOS* were exposed to reduced levels of 15 HPHCs compared to smokers who continued to smoke. The reductions in exposure to HPHCs measured in smokers who switched to *IQOS* approached the reductions observed in smokers who quit smoking for the duration of the study.
- Overall, product satisfaction and measured nicotine uptake were comparable to a cigarette, indicating that *IQOS* may be a viable alternative for adult smokers. The chart below shows the results for four primary biomarkers of exposure to HPHCs.



ClinicalTrials.gov Identifier: NCT01989156 | Results from a clinical trial conducted in the U.S. showing four biomarkers of exposure to HPHCs for adult smokers who continued to smoke, quit smoking and switched to IQOS over a 5-day period in confinement followed by 85 days in an ambulatory setting.

2. Average yield reductions of an investigational variant of *IQOS* compared to the 3R4F reference cigarette, calculated as an average of the reductions of individual HPHCs, which could be reliably quantified in the study. Aerosol collection with Health Canada's Intense Smoking Regime. All yields were taken on a mass per stick basis. Reduction calculations exclude nicotine.

Products With Reduced-Risk Potential: An innovative way to address the harm caused by smoking?

Philip Morris International's current portfolio of potentially reduced-risk products is aimed at addressing different adult consumers' preferences and includes:

- ***IQOS* Platform 2** — Heat-not-burn tobacco products
- **Platform 3 E-cigarettes** — Nicotine-containing products that contain tobacco-derived nicotine but no tobacco

Each of PMI's product platforms is designed to significantly reduce the formation of the chemicals which are widely recognized as the primary probable causes of smoking-related diseases, while providing acceptable alternatives to cigarettes for adult smokers. PMI submitted an application to the FDA in December 2016 for authorization to market *IQOS* in the U.S. as a Modified Risk Tobacco Product. In addition, the company filed a Pre-Market Tobacco Application with the FDA in March 2017.

Philip Morris International's *IQOS*

How *IQOS* Works

- *IQOS* was designed to heat tobacco with a heating blade that does not exceed 350°C. Although the heating element itself reaches 350°C, the tobacco in the Heatstick never gets to this temperature, and most of the tobacco remains below 250°C, well below the temperature required for the initiation of combustion. By contrast, cigarettes burn at temperatures of between 600°C to 800°C, exceeding 900°C during puffs.
- *IQOS* generates an aerosol and not smoke.
- The aerosol is composed mainly of water, glycerol and other vaporized substances (including nicotine and flavors) present in the original tobacco mixture.

Commitment to Science

PMI is committed to making innovative products that will benefit public health and transform the tobacco industry.

Since 2008, PMI has invested more than $3 billion in the development of a portfolio of innovative products that seek to replicate the sensorial and taste attributes of cigarettes, while delivering an aerosol that is significantly less harmful than cigarette smoke.

PMI has assembled a team of over 400 world-class scientists and engineers in key disciplines with state-of-the-art facilities in Switzerland and Singapore. It also has established a global network of research and technology partners. Since 2011, PMI has published over 200 peer-reviewed scientific publications and book chapters on the scientific assessment of products with reduced-risk potential, and all our clinical studies are registered on the public website ClinicalTrials.gov. To date, the company has over 2,350 patents granted and over 3,700 pending applications on new product developments related to candidate reduced-risk products.

PMI is committed to transparent sharing of its reduced-risk product science for unbiased verification by qualified scientists. We are confident that such evaluations of our data will support the encouraging results obtained for PMI's products so far.

Visit PMIScience.com to learn more.

August 2017

The US Food and Drug Administration (FDA) announced a comprehensive plan to improve public health by further discouraging non-smokers from using cigarettes and ensuring that adult smokers have access to less risky alternatives to cigarettes.[i]

FDA's plan, entitled, *"A comprehensive regulatory plan to shift trajectory of tobacco-related disease and deaths"* intends to apply risk-based regulation — increasing restrictions on the most risky forms of nicotine delivery (cigarettes) and allowing "greater flexibility" for noncombustible products. FDA Commissioner Scott Gottlieb's announcement speech on the plan, as well as the accompanying press release, show that:

FDA views the availability of less risky alternatives to cigarettes, including noncombustible products, as a foundational element of its plan, along with measures to reduce smoking.

"Envisioning a world where cigarettes would no longer create or sustain addiction, and where adults who still need or want nicotine could get it from alternative and less harmful sources, needs to be the cornerstone of our efforts."[ii]

"I also hope that we can all see the potential benefits to addicted cigarette smokers, in a properly regulated marketplace, of products capable of delivering nicotine without having to set tobacco on fire. The prospective benefit may be even greater for the subset of current cigarette smokers who find themselves unable or unwilling to quit."[iii]

FDA plans to apply risk-based regulation for nicotine-containing products.

For example, FDA commits to initiate a dialogue about reducing nicotine levels in cigarettes but makes it clear that this would not apply to noncombustible products. According to FDA Commissioner Scott Gottlieb:

"Looking at ways to reduce nicotine levels in cigarettes so that they are minimally or non-addictive, while not altering the nicotine content of noncombustible products such as e-cigarettes, is a cornerstone of our new and more comprehensive approach to effective tobacco regulation."[iv]

With an eye towards future regulation, FDA will seek public comment on the role that flavors (including menthol) play in attracting youth, as well as the role flavors may play in helping smokers switch to less risky alternatives.

FDA will take steps to "put […] in place the foundational regulatory elements for a comprehensive and sustainable framework for properly regulating products that may pose less risk."[v]

FDA is clear that its plan is a comprehensive package, which focuses on increasing cigarette regulation while allowing for "greater flexibility" for noncombustible products. Both components are necessary to achieve its public health goals.

"I want to emphasize that all of the steps I've outlined today are intended to work together as a package deal."[vi]

"It's only in a world where we will work to eventually render cigarettes minimally addictive that we can take on some of the other challenges or provide greater flexibility outlined here when it comes to e-cigarettes and any other noncombustible products. And we cannot pursue a plan to minimize the addictiveness and attractiveness of cigarettes if we can't simultaneously take the time to adopt additional procedural and foundational policies and regulations that are critically important to achieving our goals. That's why it's a package. And it's why we need to pursue all of these measures together."[vii]

FDA recognizes the importance of innovation, the development of less risky alternatives to cigarettes, and the role of regulation in supporting innovation:

"And we must recognize the potential for innovation to lead to less harmful products, which, under FDA's oversight, could be part of a solution. While there's still much research to be done on these products and the risks that they may pose, they may also present benefits that we must consider."[viii]

"We must also take a new and fresh look at the noncombustible side of the house. And that is why part of CTP's task is to reconsider aspects of the implementation of the final deeming rule with an eye towards fostering innovation where innovation could truly make a public health difference, and making sure we have the foundational regulations we need in place to make the entire program transparent, predictable, and sustainable for the long run."[ix]

In light of this, FDA extended the period within which manufacturers have to apply to FDA for review of noncombustible products already on the market in an attempt to encourage innovations that have the potential to make a notable public health difference.

Fundamental to FDA's approach is the continuum of risk among different methods of nicotine delivery:

"We must acknowledge that there's a continuum of risk for nicotine delivery. That continuum ranges from combustible cigarettes at one end, to medicinal nicotine products at the other."[x]

FDA recognizes that cigarettes, in particular combustion and smoke, are the primary cause of smoking related disease, not nicotine:

"Armed with the recognition of the risk continuum, and the reality that all roads lead back to cigarettes as the primary cause of the current problem, we need to envision a world where cigarettes lose their addictive potential through reduced nicotine levels. And a world where less harmful alternative forms, efficiently delivering satisfying levels of nicotine, are available for those adults who need or want them."[xi]

"The bigger problem is the delivery mechanism — how the nicotine gets delivered. Attach it to smoke particles created by burning cigarettes and the mechanism is deadly. But attach the very same nicotine to a medicinal product without the other chemicals found in tobacco products and these therapeutic products have been found to be safe and effective by FDA in helping smokers quit."[xii]

"Even with unanswered questions about the benefits and risks, there are now different technologies that deliver nicotine for those who need it that doesn't bring with it the deadly consequences of burning tobacco and inhaling the resulting smoke."[xiii]

Learn more at PMIScience.com.

i. US FDA, FDA's new plan for tobacco and nicotine regulation, July 2017, available at https://www.fda.gov/TobaccoProducts/NewsEvents/ucm568425.htm.
ii. US FDA, FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death, 28 July 2017, available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm568923.htm.
iii. FDA Commissioner Scott Gottlieb, FDA's new plan for tobacco and nicotine regulation, July 2017, available at https://www.fda.gov/TobaccoProducts/NewsEvents/ucm568425.htm; prepared remarks available at https://www.fda.gov/NewsEvents/Speeches/ucm569024.htm.
iv. Id.
v. Id.
vi. Id.
vii. Id.
viii. Id.
ix. Id.
x. Id.
xi. Id.
xii. Id.
xiii. Id.