SCIENTIFIC UPDATE

PMI SCIENCE – PHILIP MORRIS INTERNATIONAL

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SCIENCE-BASED

REGULATION

Why aerosol from our Tobacco Heating System is not smoke

U.S. regulatory landscape

Regulatory overview on smoke-free products

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INTRODUCTION

At Philip Morris International (PMI), we see smoke-free products as an opportunity which, within the right regulatory framework and with the support of society, can have a positive impact on public health. Regulating these products accordingly through a harm reduction approach is a means to seize on that opportunity. To this effect, accurate and non-misleading information and constructive debate about smoke-free products are essential for all stakeholders.

At PMI, we support an open dialogue on smoke-free products based on scientific evidence and facts, and it is with this in mind that we present in this issue the scientific evidence on the Tobacco Heating System (THS), and how the heating process affects the aerosol composition and properties, and how it is different from the cigarette smoke. Through our rigorous assessment program, we have demonstrated that THS and other smoke-free products can reduce the exposure to harmful constituents compared with cigarette smoke, and that they offer a better choice for smokers who do not quit.

In this issue we also discuss how science-based regulation can foster innovation and encourage adult smokers to switch to less harmful alternatives. Finally, we provide an overview of the regulatory landscape in the U.S., where the Food and Drug Administration (FDA) has the authority to evaluate and authorize smoke-free products. We hope that you find this issue informative, and, as always, we welcome your feedback and questions.

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EVENTS

OPEN SCIENCE

Open Science focusing on the aerosol from the Tobacco Heating System

Online

April 4, 2023

For our first Open Science event of the year, we held an online session that went live on our Open Science platform, YouTube, and on LinkedIn®. The event focused on the difference between the aerosol of the Tobacco Heating System (THS) and cigarette smoke. Two of our leading scientists, Dr. Catherine Goujon Ginglinger, Head of Chemistry Research, and Dr. Maurice Smith, Senior Scientific Advisor, shared their knowledge and expertise on PMI's aerosol research and provided a comprehensive overview of our leading heated tobacco product THS, how its emissions compare with those from cigarettes, and how the chemical analysis of its aerosol is performed.

Watch the replay here.

GLOBAL FORUM ON NICOTINE

Global Forum on Nicotine

Warsaw, Poland/Online

June 21-24, 2023

Four PMI scientists participated in the Global Forum on Nicotine (GFN) by submitting GFN Fives - 5-minute pre-recorded multimedia presentations. Ondrej Koumal discussed the "Evolution of Tobacco Sales and Use Following Introduction of Heated Tobacco Products in Japan." Carrie Wade presented "The Applicability of 'Nicotine Flux' in Tobacco Products Regulation." Christoph Neubert discussed "Barriers to Abandoning Cigarette Smoking 2022". And Anna Goralczyk presented "From Standard Toxicology to NAMs - Progress in Smoke-Free Product Assessment."

Watch the presentations from PMI scientists at GFN.

OPEN SCIENCE

Open Science: a focus on COPD

Neuchâtel, Switzerland/Online

June 26, 2023

For our second Open Science event of the year, we held a live session at our R&D Center, The Cube, in Neuchâtel, Switzerland. At the event, our speakers focused on the potential impact that smoke-free products have on chronic obstructive pulmonary disease (COPD), the third leading cause of death worldwide. The panel was composed of two leading scientific experts from PMI, Dr. Gizelle Baker and Dr. Adam Lenart, and included Dr. Tryggve Ljung from Swedish Match. Accompanying them was Prof. Riccardo Polosa of Internal Medicine at the University of Catania. Together, the panelists explored, amongst other topics, the use of oral smokeless products in Sweden and the notable reduction in the prevalence of COPD, which correlates with a decline in smoking rates. As is the case with Open Science events, the panel also answered questions live from the public.

Watch the replay here.

SCIENTIST **PROFILE**

Piotr Kozarewicz

Piotr is a Global Head in regulatory affairs for smoke-free products (SFPs) at PMI. He joined PMI in 2017 as a Regional Head Regulatory & Scientific Affairs for the EU region. Piotr is a trained pharmacist and graduated from the Medical University of Warsaw in Poland.

In his current role, Piotr leads a team responsible for the development of strategies for regulatory submissions and authorizations of SFPs. In doing so, he and his team provide expertise and guidance on regulatory matters throughout the lifecycle of SFPs, from early development and market access to post-market activities. As a pharmacist, Piotr is a believer and keen advocate of tobacco harm reduction strategies and supports PMI's ambition to deliver a smoke-free future.

REGULATORY OVERVIEW ON SMOKE-FREE PRODUCTS

Regulations on smoke-free products such as heated tobacco products, e-vapor products or e-cigarettes, snus, and oral nicotine pouches vary significantly worldwide, reflecting the diverse approaches governments take to address the complex health and societal challenges associated with their use. This article delves into the multifaceted landscape of regulations across the globe, highlighting some trends and noteworthy policies.

Tobacco harm reduction as a part of regulatory approach

Looking back at how governments have tackled the issue of smoking, the focus has primarily been on traditional prevention and cessation strategies. Although, the idea of regulating tobacco products originated in the 1960s with reports from the U.K. Royal College of Physicians and U.S. Surgeon General on Smoking and Health, regulatory policies have since then followed identifiable trends, including advertising restrictions, limiting the areas where one may use such products, health warnings, taxation, and more.

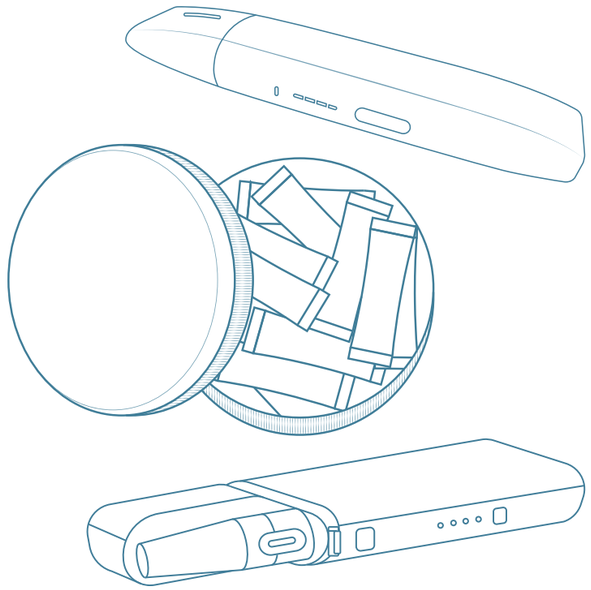
During the late 1990s, a group of global tobacco control experts was convened by the World Health Organization (WHO) and asked to explore how to strengthen efforts to reduce the harm caused by smoking. This group recommended that complementing prevention measures and cessation support programs with a harm reduction approach would significantly reduce smoking-related harm in future generations. A harm reduction approach can help adult smokers who would otherwise continue to smoke to have access to scientifically substantiated smoke-free products that are available today as a result of significant advances in technology and science.

More and more governments around the world have adopted the principles of harm reduction in their tobacco policies and have recognized that smoke-free products can have a role to play in reducing the harm caused by smoking. These governments are complementing traditional tobacco control measures such as those intended to discourage initiation and encourage cessation of smoking, with harm reduction approaches such as providing adult smokers that do not quit with information about, and access to, scientifically substantiated smoke-free products to accelerate the move away from cigarettes. Countries such as New Zealand and Czechia officially embraced a harm reduction approach as a complementary policy to address the issue of smoking and accelerate its decline. In the U.S., Italy, Bulgaria, Cyprus, Portugal, and Greece, regulators have adopted regulatory frameworks defining the scientific requirements for the communication towards the consumers about reduced-risk or reduced-harm effects of innovative tobacco products compared with smoking.

Categorizing smoke-free products

Many countries have updated their existing regulatory frameworks to regulate novel smoke-free products under unique or dedicated product categories. These categories include a level of differentiation compared with combustible tobacco products, including differentiated health warnings, flavor and packaging requirements, and others. This approach recognizes that not all tobacco products are equally harmful. Indeed, nicotine-containing products fall on a continuum of harm, with cigarettes at the highest end of the continuum.

Heated tobacco products (HTPs) have a significant potential to serve as an acceptable alternative for adults who would otherwise continue to smoke. HTPs, also known as heat-not-burn products, are a category of products that heat the tobacco instead of burning it. The aim is to substantially reduce the emission of harmful chemicals in HTPs as compared with cigarette smoke. This innovative and evolving category includes products that vary with respect to temperature, heating source,



or the way the tobacco may be processed. While not risk free, HTPs can be a better alternative to smoking, and they should be made available to adult smokers who would otherwise continue to smoke.

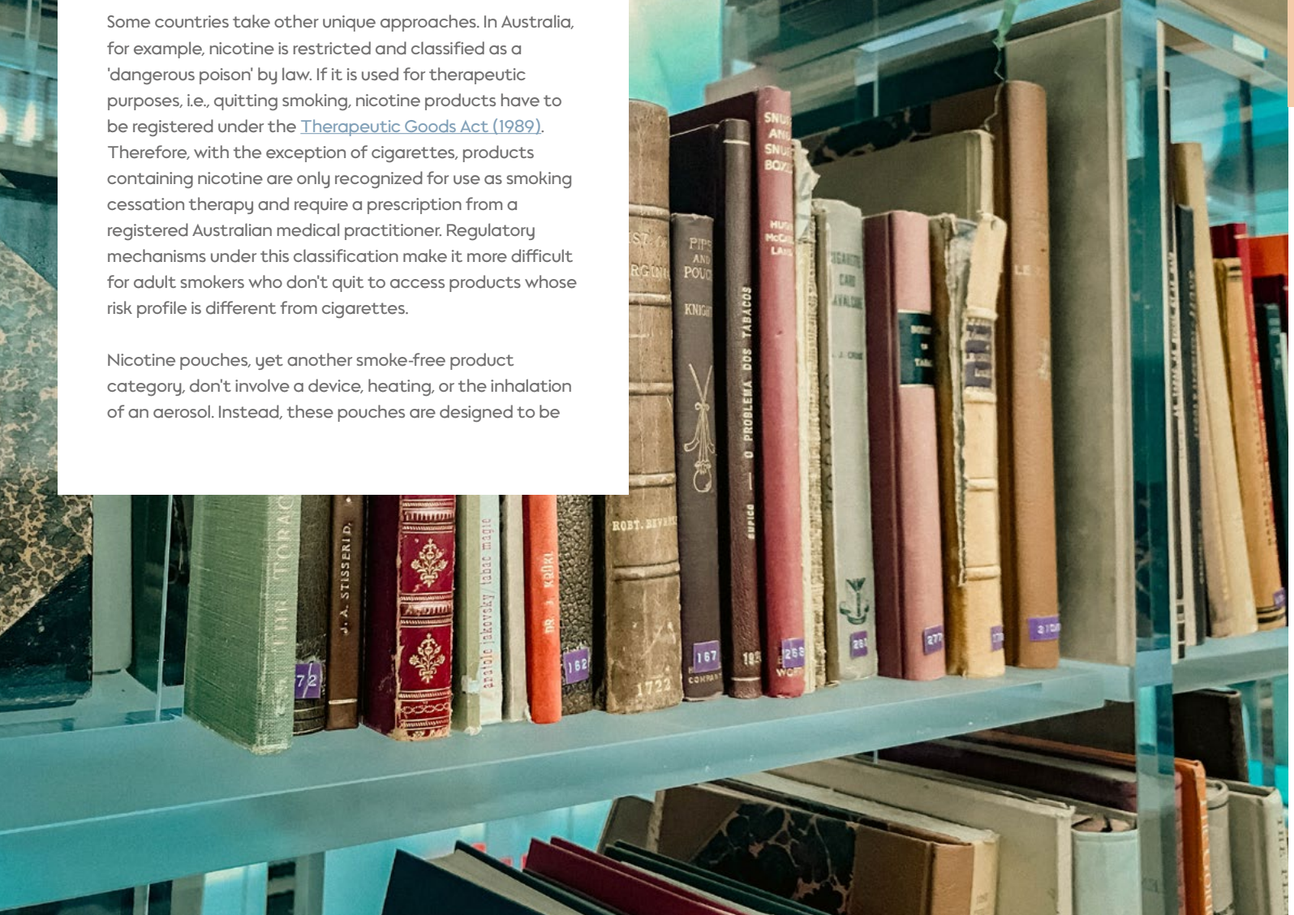
Following a similar trend, e-vapor products are also classified as a unique product in many countries and regions. New Zealand or the EU—which has implemented the Tobacco Products Directive (TPD)—are examples of countries or regions which acknowledge that HTPs and e-vapor products are different from cigarettes. However, there are also countries that take a more excessive approach and ban smoke-free products altogether, effectively allowing in the market only the most harmful form of consuming nicotine, i.e., cigarettes. Examples include India, Turkey, or Brazil.

On the other hand, there are also countries which have taken the approach of regulating smoke-free products the same as combustible products. This approach limits or outright bans the communication with adult smokers, which makes it hard for them to make informed decisions. These approaches disregard the potential role that scientifically substantiated smoke-free products can have in moving adult smokers who don't quit away from cigarettes, which is the most harmful way of nicotine consumption.

Some countries take other unique approaches. In Australia, for example, nicotine is restricted and classified as a 'dangerous poison' by law. If it is used for therapeutic purposes, i.e., quitting smoking, nicotine products have to be registered under the Therapeutic Goods Act (1989). Therefore, with the exception of cigarettes, products containing nicotine are only recognized for use as smoking cessation therapy and require a prescription from a registered Australian medical practitioner. Regulatory mechanisms under this classification make it more difficult for adult smokers who don't quit to access products whose risk profile is different from cigarettes.

Nicotine pouches, yet another smoke-free product category, don't involve a device, heating, or the inhalation of an aerosol. Instead, these pouches are designed to be placed between the upper lip and gum, allowing nicotine absorption through oral mucous membranes before entering the bloodstream.

From a regulatory point of view, the approach to oral nicotine pouches varies. They are commercialized in the U.S., the U.K., and various countries in Europe. In the EU, the regulatory classification of nicotine pouches is not harmonized (i.e., not subject to EU directives) with some EU countries, explicitly or implicitly, banning the commercialization of nicotine pouches altogether (Belgium and the Netherlands), while others regulate them such as Czechia, Slovakia, Sweden, Denmark, Iceland, and Norway. Pending regulations are in progress in various countries across Europe such as Finland to more clearly integrate nicotine pouches within the tobacco product regulations.



Refocusing regulatory attention to the primary cause of the health harms of smoking, which is combustion, and the ways these harms can be mitigated could have a positive impact on public health.

An evolving regulatory landscape

New technologies continue to emerge, and regulations must continue to adapt at a rapid pace. In the heat-not-burn category, new products have been introduced which contain nicotine without tobacco, or which are based on other ingredients and do not contain either nicotine or tobacco. In fact, new production methods have even made it feasible for some companies to produce products with synthetic nicotine, or even which contain nicotine analogues like metatin, placing them outside the regulatory framework in some countries.

Priorities among health agencies and countries continue to change in response to these emerging products. The global discussion on tobacco regulation has seen a shift from a focus on tobacco and its health harms to zero in on nicotine instead. Nicotine is indeed addictive and not risk free, but it is not the primary cause of smoking-related disease. Refocusing regulatory attention to the primary cause of the health harms of smoking, which is combustion, and the ways these harms can be mitigated could have a positive impact on public health.

Another priority shift, or perhaps inconsistency, that has been seen is the promotion of public health policies that outright ignore tobacco harm reduction approaches. Consider the WHO Framework Convention on Tobacco Control (FCTC), where harm reduction is defined as a strategy of tobacco control. Despite this definition, harm reduction is absent from the recommendations of the WHO.

One important aspect of public health which several countries are already addressing is the importance of regulation that safeguards against access to tobacco and nicotine-containing products for underage users. These regulations will require the precision to balance these safeguards while ensuring that adult smokers who don't quit are not prevented from accessing products that are better than continued smoking.

In the midst of this changing regulatory landscape, the primary role of regulation remains the same: protecting the health of the public. The reliance on data and scientific evidence to make informed policy decisions, and a harm reduction approach that sees the most harmful products being subject to the most restrictive regulations, have the potential to see the greatest impact on public health.

WHY AEROSOL FROM OUR TOBACCO HEATING SYSTEM IS NOT SMOKE

It is common knowledge that smoke derives from combustion, and that the absence of combustion generally equates to the absence of smoke. Despite this, the topic is still heavily debated, especially outside of the scientific community. In this article, we focus on smoke, what is it, how is it formed, and why its absence is critical for smoke-free products such as Tobacco Heating System (THS)*.

Why smoke is the main problem

The harms of cigarette smoking are well known. Smoking-related harm and disease are caused by long-term exposure to the toxicants in cigarette smoke. For current smokers, the best step they can take to reduce their risk of harm is to quit tobacco and nicotine use altogether. But the fact is that not every smoker quits.

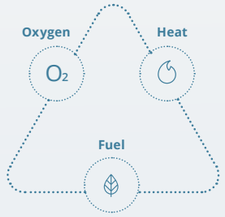
As part of the tobacco harm reduction approach, alternatives to cigarettes have been developed such as the THS. THS does exactly what its name suggests: it heats tobacco instead of burning it. That is the fundamental difference between THS and cigarettes. By not burning tobacco, we have shown that THS doesn't create smoke, but instead, a non-smoke aerosol which, while still not risk free, contains significantly fewer and lower levels of harmful chemicals compared with cigarette smoke.

** Commercialized as IQOS*

The scientific definition of smoke

Smoke, according to the scientific consensus, is an aerosol formed during combustion and high-temperature pyrolysis which contains liquid and solid particles also known as particulate matter as well as gases.

The particulate matter found in smoke is formed when products of combustion and high-temperature pyrolysis reach high enough concentration (specifically, they reach supersaturation) to nucleate via condensation or interact with each other to form particles. In particular, the carbon-based solid particles found in smoke (also known as soot) are formed from high concentrations of certain chemicals acting as precursors, such as polycyclic aromatic hydrocarbons, that are produced only at the high temperatures associated with combustion.



Combustion

How is cigarette smoke formed?

Cigarette smoke is a product of combustion, which is defined as a chemical process of oxidation that occurs at a rate fast enough to produce heat and usually light in the form of either a glow or flame. Combustion also includes both complete and incomplete (partial) combustion processes, such as smoldering (flameless) and flaming combustion.

The combustion of a cigarette takes place after ignition, when temperatures in a cigarette exceed about 400 °C. It then becomes self-sustaining as long as the exothermic (heat-generating) oxidation reaction is sufficiently strong to overcome heat losses and endothermic (heat consuming) processes, such as vaporization and endothermic thermal decomposition.

During combustion, particulate matters are formed when combustion products reach high enough concentration to nucleate via condensation, or when they interact with each other to form liquid particulate matter (droplets) and solid particulate matter such as soot.

What is in cigarette smoke?

Cigarette smoke is a complex and dynamic chemical mixture that has been well characterized, with billions of carbon-based solid particles (soot) and more than 6,000 constituents identified. Within this complex mixture, about 100 constituents have been associated with smoking-related disease by public health authorities. These constituents are also known as harmful and potentially harmful constituents (HPHCs).

Why is the aerosol from THS not smoke?

While smoke is an aerosol, not all aerosols are smoke. The aerosol from THS contains droplets which are not formed from the condensation of byproducts of combustion or pyrolysis. Instead, these droplets are generated when glycerol—added to the tobacco material during processing as an aerosol former—is vaporized and reaches supersaturation, leading to its condensation during the cooling phase and the formation of nuclei, onto which more glycerol, as well as water, nicotine, and other constituents can condense to form liquid aerosol droplets.

Thus, aerosols formed from THS are not smoke as they are very different in terms of origin and chemical and physical composition to the smoke formed from the combustion and associated high-temperature pyrolysis products generated from the burning of tobacco. Furthermore, we have conducted several research studies substantiating that no combustion of the tobacco material occurs in our THS and that our THS aerosol is liquid-based and is not smoke.

Actually, the aerosol generation process in THS is equivalent to the aerosol generation process in most e-vapor products, for which aerosol formers (glycerol and propylene glycol) in the e-liquid are vaporized during heating and are subsequently cooled down to form liquid aerosol droplets.

Why doesn't THS need oxygen to work?

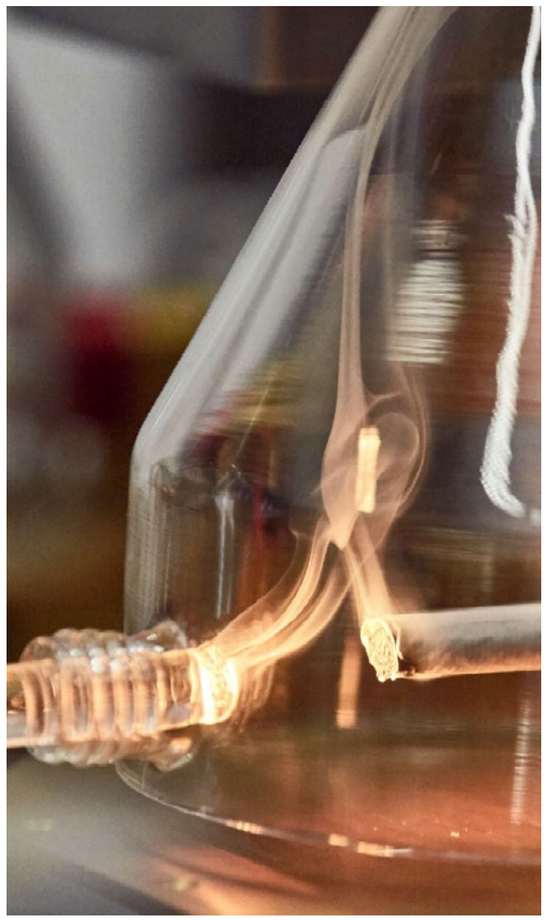
THS doesn't need oxygen to work because there is no combustion (oxidative process) as the tobacco material is heated to temperatures below ignition. In fact, the tobacco material within THS undergoes processes such as drying and vaporization, as well as thermal decomposition (torrefaction and low-temperature pyrolysis) which are not associated with combustion, either complete or incomplete.

Furthermore, the comparison of the chemical composition of THS aerosol generated in oxidative (air) and non-oxidative (nitrogen) environments indicates that oxygen—necessary for combustion to happen—does not play a major role in the thermal decomposition of the tobacco material in THS or the aerosol formation.

The absence of combustion in THS has been substantiated by scientific evidence and has been verified by third-party scientific experts in numerous countries as well as by independent research organizations.

By eliminating combustion in our tobacco-containing smoke-free products, we aim to drastically reduce the formation of HPHCs and to generate a liquid-based aerosol without the billions of carbon-based solid particles being a hallmark of smoke. Our principle is to heat tobacco to temperatures low enough to avoid ignition and burning. This allows nicotine and flavors to be released from the tobacco, while generating significantly lower levels of HPHCs compared with cigarette smoke.

It is to note however, that THS is not risk free and contains nicotine which is addictive.



> *Our principle is to heat tobacco to temperatures low enough to avoid ignition and burning. This allows nicotine and flavors to be released from the tobacco, while generating significantly lower levels of HPHCs compared with cigarette smoke.*

Does THS aerosol contain solid particles like in smoke?

In smoke, billions of carbon-based solid particles or soot, are typically produced during combustion, and inhaling them has been shown to trigger inflammation and to cause lung and cardiovascular disease. Our THS has been proven not to produce these carbon-based solid particles by our research as well as by numerous peer-reviewed publications by various research groups. So, there are no solid particles in the aerosol produced by THS.

As we have seen throughout this article, smoke is a product of combustion or high-temperature pyrolysis. And the smoke generated by these processes contains billions of carbon-based solid particles (soot) as well as high levels and numbers of harmful chemicals.

Smoke-free products, such as THS, do not combust tobacco and therefore do not generate smoke.

U.S. REGULATORY LANDSCAPE

While the commercialization of a number of new tobacco and nicotine-containing products has been authorized in the U.S. market for almost a decade, the regulatory landscape in the U.S. faces a series of challenges that, if not overcome, may influence the adoption of these products by adult smokers wishing to move away from cigarettes and their potential impact on public health. In this article, we examine some key regulatory milestones for the commercialization of tobacco and nicotine-containing products in the U.S., as well as two significant challenges in the U.S. regulatory landscape.

Why regulations on smoke-free products matter

In the interest of tobacco harm reduction, adult smokers and nicotine users need accurate and non-misleading information about smoke-free products. As we have learned, product information can help them to switch more completely. The U.S. is an example of a country where there are regulatory pathways that are required for the commercialization of and communication about novel smoke-free products, an approach that can help to ensure there is clear substantiation behind statements made across the product category. Despite some of the successes of this approach, the implementation can be complicated. Here, we provide examples from our own applications.

Key milestones and what they reveal

November 2015 was a major milestone within the tobacco industry. It saw the clearance by the U.S. Food and Drug Administration (FDA) of the first tobacco products to be commercialized under the premarket tobacco product application (PMTA), a legal requirement for the introduction of any novel tobacco-containing product into the U.S. market. These products were eight snus smokeless tobacco products sold under the *General* brand name, by Swedish Match USA, Inc., now a PMI company. While snus was already available in the U.S. market through a number of companies, the eight *General Snus* products were the first to go through this formal review. Submitted on March 11, 2015, the PMTA took 236 days to be authorized by the FDA, well within expected timeline.

With the PMTA review completed, focus then turned to the Modified Risk Tobacco Product (MRTP) review for *General Snus* products, the application for which had been submitted in June 2014. An MRTP authorization allows the specified product to be marketed with reduced-risk related information. The MRTP review by the FDA took 1,961 days to complete, and in October 2019, the use of the following claim was authorized: "Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

MRTP authorizations are valid for up to 5 years, which means that the MRTP authorization for *General Snus* products will expire in October 2024. Thus, an MRTP renewal application was submitted in July 2023 by Swedish Match. In November 2023, the FDA completed a preliminary review of this application and determined that it met the filing requirements for a tobacco product seeking a modified risk order. As a result, the application was filed and entered the substantive review phase. In early December 2023, the FDA opened a docket and invited public comments on the renewal of existing MRTP orders. At the time of writing, the FDA has not established a closing date for the comment period. The next stage will involve the referral of the MRTP application to the Tobacco Products Scientific Advisory Committee (TPSAC), a group of experts in medicine, medical ethics, science, or technology involving the manufacture, evaluation, or use of tobacco products. No closing date has been communicated for this next stage as well.

In May 2017, PMI submitted the PMTA for the tobacco heating system, THS 2.2, commercially known as *IQOS 2.4*. The FDA granted its authorization—the first heated tobacco product to be authorized under the PMTA in April 2019. The review of the MRTP application for the same product followed.

Submitted in 2016, the MRTP review was completed in July 2020, and PMI was authorized to use the following statements:

1. The IQOS system heats tobacco but does not burn it.
2. This significantly reduces the production of harmful and potentially harmful chemicals.
3. Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

This MRTP authorization has a four-year expiration date, which ends in July 2024, and an MRTP renewal was submitted by PMI in July 2023. The FDA accepted this renewal application in September 2023, but did not provide any further response at the time of writing.

Milestones in U.S. Tobacco Regulation for *General Snus* and THS 2.2

An increasingly unpredictable market

One key challenge in the U.S. regulatory environment for tobacco products is the unpredictability in the time it takes the FDA to review marketing applications. PMTA authorizations have been granted by the FDA for 45 products so far, yet around half a million PMTAs are pending review at the FDA, with PMI applications among them. For example, PMTAs for Swedish Match's oral nicotine products *ZYN Flagship* and *ZYN Ultra* have not been processed despite being submitted in March 2020 and November 2021, respectively. The FDA has started reviewing the PMTA for only one variant so far.

In October 2023, PMI submitted PMTAs and MRTP applications for a new variant of THS, THS 3.0 commercialized as *IQOS Iluma*, and the accompanying tobacco sticks commercialized as *TEREA*. At the time of writing, the FDA has not yet confirmed the acceptance of these applications.

As the industry continues to push forwards with innovative smoke-free products, it is becoming increasingly difficult to predict when these products will be allowed to be commercialized in the U.S. market.

As we have seen, the biggest challenge in the U.S. regulatory environment for tobacco products is the unpredictability in the time it takes the FDA to review marketing applications.

Unclear evaluating standards

Another challenge in the U.S. is the standards by which the FDA grants authorizations under the PMTA and MRTP pathways. While the FDA makes its assessments based on the risks and benefits of a tobacco product to the population, including both users and non-users of tobacco products, the requirements for these assessments are available in draft format only and subject to change, for the MRTP process for example, leaving the opportunity for shifting priorities.

Because of the current ambiguities around the assessment process, PMI has sought out regulatory experts on the scientific evaluation of tobacco product applications at the FDA to guide us through these applications, and even then, the process remains difficult.

As the industry continues to evolve and brings forth more innovative products, the regulatory landscape must adapt to support its growth. Through PMTAs and MRTP applications, the regulatory approach taken by the U.S. has already embraced the harm reduction approach to complement prevention and cessation strategies linked to smoking cigarettes. Such an approach allows more adult smokers to choose lower risk options instead of continuing to smoke, which can have a positive impact on population harm. Reducing authorization timelines and clarifying standard requirements would be important for this approach to truly take hold in the U.S. and make a significant impact on public health.

Dr. Matthew Holman

Matthew, VP and Chief Scientific & Regulatory Strategy Officer in PMI's U.S. offices, worked for more than 20 years with the U.S. Food and Drug Administration (FDA), most recently as Director of the Office of Science at the Center for Tobacco Products (CTP).

PMI PUBLICATIONS

Preliminary toxicological assessment of heated tobacco products: A review of the literature and proposed strategy

Heated tobacco products (HTPs) have become increasingly common in many countries worldwide. Yet, there is limited guidance from tobacco product regulations concerning the requirements for performing preliminary toxicological assessments to ensure that the design of the product does not lead to any unintentionally increased or new risk, compared with the traditional products that consumers seek to replace. The purpose of this paper is to describe an approach for preliminary toxicological assessment of HTPs which is a necessary step before evaluating their reduced-risk potential compared with conventional cigarettes. The authors reviewed the literature on HTPs and propose a 3-phase strategy for the preliminary toxicological assessment: (1) identification and hazard assessment of all substances and materials in the product; (2) exposure assessment based on product use; (3) aerosol chemistry analysis and *in vitro* toxicology assessment of the final product or flavor mixture. The authors conclude that such a strategy could provide consistent and reliable data for manufacturers and regulators to ensure that HTPs do not present novel or increased hazards in comparison to smoking cigarettes.

Recommendations on the optimal methods for conducting *in vitro* assays to assess the toxicity of tobacco and nicotine products

This publication reports the summary and recommendations of the third workshop sponsored by the Institute for In Vitro Sciences (IIVS) on the use of *in vitro* methods for evaluating tobacco products, especially next generation nicotine and tobacco products (NGPs). The workshop focused on the challenges and best practices for generating and testing different types of samples from combustible cigarettes, heated tobacco products (HTPs), and electronic nicotine delivery systems (ENDS). The workshop participants and authors of this document include experts from tobacco companies including PMI, contract research organizations, the U.S. Food and Drug Administration, academia, and other *in vitro* assay specialists.

The workshop outcomes included consensus terminology and graphics for various sample types, as well as specific recommendations for each sample type regarding sample preparation, characterization, dosimetry, exposure methods, and data interpretation. The workshop also highlighted the need for greater standardization, optimization, and contextualization of the *in vitro* methods for tobacco product evaluation.

Investigating the toxicity of unregulated e-liquids and the impact of high-power levels used in e-vapor products

The safety of e-vapor products, which are battery-powered devices that deliver aerosolized propylene glycol and vegetable glycerin (PG/VG) as well as flavorings with or without nicotine, can be influenced by the presence and concentration of unregulated chemicals and the device power settings. This study used human macrophage-like and bronchial epithelial cell cultures to investigate the toxicity of homemade e-liquids containing PG/VG, nicotine, vitamin E acetate (VEA), medium-chain fatty acids, phytol, and cannabidiol (CBD). The study also exposed SmallAir™ organotypic epithelial cultures to aerosols from adulterated e-liquids generated at different power settings.

The results showed that CBD, phytol, and lauric acid caused cytotoxicity and increased lipid-laden macrophages, while treatment with nicotine or VEA alone or with PG/VG did not impact cell viability. Aerosols generated with higher power settings had higher carbonyl concentrations. The study concluded that the addition of specific unregulated e-liquid components and the use of high-powered devices may produce compounds that could cause consumer health and safety issues, and suggested the need for regulation and standardization of e-vapor products and their toxicological risk assessment.

Tobacco heating system (THS) has less impact on bone metabolism than cigarette smoke

Cigarette smoking has been shown to negatively affect bone fracture healing. However, the use of THS on fracture healing has not been comprehensively investigated. The goals of this study were to develop an *in vitro* system for studying bone metabolism (how bone grows and how it is repaired) and to compare the effects of THS with cigarette smoke on *in vitro* fracture healing. The study showed that following acute or chronic exposure to particulate matter extract from THS aerosol, the THS was less harmful to the bone coculture system than reference cigarette smoke extract. In the fracture healing model, cultures exposed to the THS extract maintained similar osteoclast activity and calcium deposits as control cultures. Conversely, smoke extract exposure promoted osteoclast activity, resulting in an osteoporotic environment.

The nicotine concentration was the same in the THS aerosol and cigarette smoke exposure groups in this study, suggesting that the high level of toxicants generated by smoke and not nicotine itself is the main cause for impaired bone healing.

The importance of perceived risks in the adoption of heated tobacco products amongst adult smokers

This study investigated how the perceived reduced formation of harmful chemicals (RF) and perceived reduced risk of harm (RH) of the heated tobacco product (HTP) *IQOS* influenced the exclusive and stable exclusive use among adult smokers in four countries. The authors used data from longitudinal online surveys of HTP users who were followed up for 48 weeks. The results show that HTP users who indicated reduced formation of harmful chemicals or reduced risk of harm as reasons for using HTP were more likely to switch completely and stably to HTP than those who did not. Also, RH seems to be a stronger driver than RF for complete switching to exclusive HTP use. The authors conclude that accurate and truthful communication of the reduced harm of HTPs may facilitate smokers' switching from combustible to smoke-free products.

Meta-analysis on the effects of smoking and smoking cessation on triglyceride levels

Smoking increases lipid levels, including triglycerides, which are associated with cardiovascular disease risk. This study aimed to quantify the effects of smoking and smoking cessation on triglyceride levels. A meta-analysis was conducted on 169 studies evaluating the effects of smoking on triglyceride levels and 21 studies evaluating the effects of smoking cessation on triglyceride levels. The results showed that smokers had significantly higher triglyceride levels than nonsmokers, but the effect varied widely across studies. Smoking cessation was associated with a slightly significant decrease in triglyceride levels at 1 month, but no significant difference at other follow-up durations. The authors concluded that smoking is clearly linked to higher triglyceride levels, but the impact of quitting on triglyceride levels needs further investigation.

PMI SCIENCE

PHILIP MORRIS INTERNATIONAL

Important information

This Scientific Update provides an overview of the most recent scientific developments behind PMI's approach to achieving a smoke-free future through a range of alternatives to cigarettes that do not burn tobacco. The text in these pages include our product development and assessment efforts, our initiatives to share our methodologies and results, as well as our publications.

More detailed information can be found at www.pmiscience.com.