SCIENTIFIC UPDATE

PMI SCIENCE – PHILIP MORRIS INTERNATIONAL

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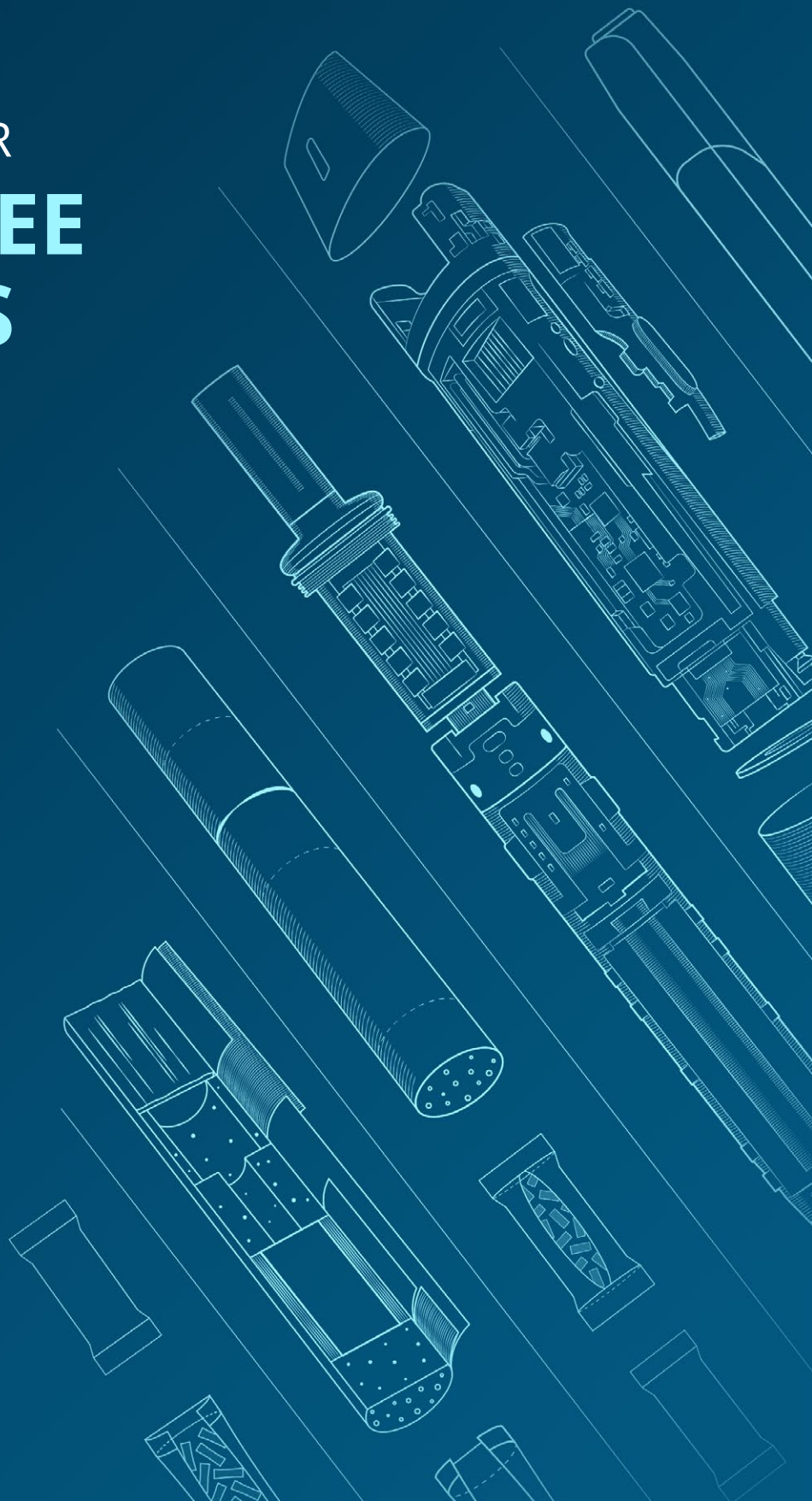
A LOOK INSIDE OUR

SMOKE-FREE PRODUCTS

Introducing oral **nicotine pouches**

How tobacco sticks **are made**

A growing range **of smoke-free products**



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INTRODUCTION

Quitting tobacco and nicotine altogether is the best choice someone who smokes can make. But we all know that not everybody does. Adult smokers who don't quit deserve access to, and information about, better alternatives to cigarettes. Robust product science and technology is at the core of our efforts to develop a range of smoke-free alternatives that addresses the needs of smokers who would otherwise continue to smoke. Our smoke-free products are broken into three main categories: heat-not-burn, e-vaping and oral smokeless, and all of them provide nicotine without burning tobacco in various ways. Product science enables product understanding, so that we can design and develop more relevant products faster and demonstrate the harm reduction potential of these products.

In this issue, we show how tobacco sticks are made to facilitate the heating rather than burning of tobacco. We also discuss the introduction of oral nicotine products to our range of smoke-free products, and the available science on this category of products. With an increasing variety of better alternatives to cigarettes becoming available, adults who smoke will have a greater chance to find something that works for them.

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EVENTS

SCIENTIFIC
SUMMIT

Scientific Summit on Tobacco Harm Reduction

Online, Athens

September 21-22, 2022

Two PMI scientists participated in the 5th Scientific Summit on Tobacco Harm Reduction: Novel products, Research & Policy, which took place virtually and in Athens, Greece. The conference included topics on toxicology and aerosol chemistry, preclinical evaluation, epidemiology and social issues, bioethics, and novel products.

Suzana AlMoosawi presented on 'Risk perception of *IQOS*: Evidence from Japan's rolling post-market cross-sectional surveys'. Karina Fischer discussed 'Perceived reduced formation of harmful chemicals (RF) and perceived reduced risk of harm (RH) impact exclusive use of heated tobacco product *IQOS*: A prospective consumer cohort study in four culturally and socio-economically different countries'.

Learn more about the conference here.

Watch the presentations from PMI scientists at the Scientific Summit

OPEN **SCIENCE**

Open Science, Live from the Cube

Neuchâtel / Online

December 6, 2022

Our ninth Open Science event was held live in December at our R&D Center, The Cube, in Neuchâtel, Switzerland. It focused on innovative products behind a smoke-free future and the alternatives to cigarettes that are available for adults who would otherwise continue to smoke. Our scientific experts, Gizelle Baker, Mathias Beutler, Davide Sciuscio, and Robert Emmett, took part in a panel discussion and a question-and-answer session. Topics included the science and technology behind our smoke-free products, and the scientific research that has already been done to assess the risk profile of these different products. Participants also attended virtually on our Open Science platform and on LinkedIn.

Watch the replay here.

SCIENTIST **HIGHLIGHT**

Dr. Patrick Vanscheeuwijck

Patrick is Vice President, Smoke-Free Products Category in Life Sciences, and joined PMI in 1995 as a Bioresearch Manager in a PMI research laboratory. He holds a Post-doctorate in Molecular Biology from KU Leuven, a Post-doctorate in Molecular Pharmacology from the University of Arizona, a PhD in Biochemical Pharmacology and a master's in Science, Biochemistry, from Ghent University.

At PMI, Patrick has held various positions, including as General Manager of two PMI research laboratories, specializing in experimental biology and toxicology, chemistry, *in vitro* and *in vivo* toxicology, and Director, Pre-clinical Toxicology. He spent the first part of his career at PMI developing and applying preclinical science to support the early development of the smoke-free products category. He has published numerous articles in international scientific journals.

A GROWING RANGE OF

SMOKE-FREE PRODUCTS

As we work towards a smoke-free future, there is an increasing need to give adult smokers who would otherwise continue to smoke alternatives to cigarettes.

PMI's range of smoke-free products

We have a vision of replacing cigarettes with better products for adults who smoke and won't quit. To achieve this, we need to meet the range of needs and preferences of adult smokers. This is why we are developing a range of smoke-free products.

At Philip Morris International (PMI), our products involve inhalable and non-inhalable approaches to nicotine delivery, some of which contain tobacco while some do not. With a few exceptions, all our smoke-free products contain nicotine, which is addictive and not risk-free. Most of our smoke-free products fit into the inhalable category, because they produce an aerosol that is inhaled as part of the user experience.

Heated tobacco products, such as the Tobacco Heating System (THS), heat tobacco instead of burning it. This is done via an electronically controlled system using either resistive (THS 2.2) or inductive (THS 3.0) heating technology. We also recently introduced the Oven Heating System (OHS). Unlike THS, which heats the tobacco internally, OHS heats the tobacco from the outside of the tobacco stick. In agreement with the South Korean company KT&G, PMI also commercializes the Pin Heating System (PHS) and he Aerosol Heated Tobacco System (AHTS) outside of South Korea.

Also among the inhalable category, we offer several e-vapor products that use different aerosol generation technologies. We developed the MESH Vaping System (MVS), which uses our e-vapor mesh technology. This technology addresses certain challenges presented by some e-vapor products currently on the market.

We have also developed a Disposable Vaping System (DVS), which requires no charging, cleaning, or refilling.

We have also explored different technologies to mechanically produce a nicotine-containing aerosol without tobacco, combustion, or heating. The result is the Nicotine Salts Product (NSP), which is a nicotine-based electronics-free product.

Besides inhalable products, we've added oral products to our portfolio too. One example is the oral nicotine pouch produced by the Danish company AG Snus, a company that was acquired by PMI in 2021. Oral nicotine pouches are placed between the gum and the cheek or upper lip, where nicotine is absorbed through the oral mucosa.

The science behind smoke-free products

The logic behind the development of smoke-free products is centered on the problem of burning. The process of burning tobacco creates smoke, which contains thousands of chemicals. Many of those chemicals are harmful or potentially harmful. By heating tobacco at lower temperatures, heated tobacco products avoid burning the tobacco, and thus don't create smoke.

The aerosol produced by our inhalable smoke-free products contains lower average levels of harmful chemicals compared to those found in cigarette smoke, and they also do not produce ash or carbon-based solid particles. We've described in detail how THS emits an aerosol that contains on average around 95% lower levels of harmful chemicals compared to the smoke of a reference 3R4F cigarette. And our oral nicotine products produce no emission at all for a user to inhale. Importantly, a reduction in the emission of harmful chemicals (or a lack of emission altogether) does not equal a reduction in risk. No smoke-free product is risk-free.

Our product assessment approach includes studies of the products' aerosol (and comparable studies for oral products), toxicological effects, clinical outcomes, consumer perception and behavior, as well as longer-term studies of products once they're available in the market. You can find the studies and presentations by PMI scientists in our publications library on PMIScience.com. We have also gathered a list of independent research on smoke-free products, though it is by no means an exhaustive list as the number of studies is growing rapidly.

More options for smokers looking for better alternatives

In the interest of reducing the harms of smoking to the population, the more people who quit smoking altogether, the better. It's the best choice a smoker can make. For those who don't quit, an increase in the number of people who switch to a product that presents less risk of harm compared to cigarettes is also a step toward reducing harms of smoking to the population.

Adults who smoke currently have access to a wide variety of cigarettes to choose from. Those who want to switch to a product that is a better alternative than cigarettes should have access to a variety of smoke-free options as well.

Having more options makes it much easier to find an alternative that works for each individual, so they can switch completely and leave cigarettes behind.

The increase in variety of smoke-free products available to choose from carries with it another benefit that could encourage smokers to switch: variety in price. While product pricing isn't part of our assessment program, certainly the cost of the product might influence a smoker's choice to try and completely switch to a smoke-free alternative to cigarettes.

As we continue to add to our range of smoke-free alternatives to cigarettes, we'll continue to scientifically assess our products to better understand their risk reduction potential. And we'll continue to communicate our findings as they become available. In this way, we'll do our part to provide accurate scientific information about our growing range of smoke-free products.

NICOTINE POUCHES

JOIN PMI'S SMOKE-FREE PRODUCT PORTFOLIO

Nicotine pouches have been introduced to our range of smoke-free products. In this article, we describe how they are consumed and share some of the latest scientific research that's available.

Smoke-free product portfolio

We at Philip Morris International (PMI) have a vision of replacing cigarettes with better products for adult smokers who don't quit smoking. To achieve this, we need to meet the range of needs and preferences of adult smokers who would otherwise continue to smoke. This is why we are developing a range of smoke-free products, with a variety of ways to provide nicotine for adult smokers and adult nicotine users, without burning tobacco.

The potential impact of smoke-free products on public health has already started to surface: as Heated tobacco products have led to an accelerated reduction in cigarette sales in Japan.

In Norway and Sweden, two countries where snus is legally available for many years, the product has gradually replaced cigarettes and is now the predominant form of nicotine use. According to Statistics Norway, the percentage of daily smokers dropped from 25% in 2005 to 8% in 2021 while snus users increased from 5% to 15% in the same time frame. In Sweden and Norway, men switched from cigarettes to snus gradually over generations while the women in these countries started to switch later. The men there have lung cancer mortality rates that are among the lowest in EU countries according to the IARC, Cancer Today.

No one product will address all adult smokers' or nicotine users' individual preferences. Clearly, a range of alternatives is key to helping adult smokers who don't quit to move away from cigarettes.

Introducing oral nicotine pouches

At PMI, we have added a new category to our range of smoke-free products: oral smokeless products. One example from this category is our nicotine pouches commercialized under the *Shiro* brand. These pouches are tobacco-free products containing a powder consisting of nicotine and other ingredients. The pouch should be placed between the gum and upper lip. Nicotine pouches are smoke-free products that, by design, do not burn tobacco and create no aerosol or smoke at all.

The high purity, pharmaceutical grade nicotine in the pouches is extracted into the saliva and is absorbed mainly via the mucous membranes in the mouth before entering the blood stream. Some nicotine can also reach the gastrointestinal tract if the saliva is swallowed.

PMI nicotine pouches

POUCH
The nicotine pouch is made from organic cellulose compounds that create a non-woven fleece. The pouch serves as a container for the nicotine-containing substrate.

FLAVORS
The substrate includes E-numbered food-grade flavors, with most nicotine pouches having a mint flavor.

NICOTINE
The nicotine is a pharmaceutical grade nicotine, extracted from tobacco plants.

pH BUFFER
If the pH level is too neutral, then nicotine won't transfer across the mucosa. Anything above 9.1 becomes too basic and can be a strong mucosal irritant, which is why existing industry standards set that upper limit. Sodium carbonate or bicarbonate is commonly used to regulate the pH.

BINDER/FILLER
The binder/filler helps determine the speed of nicotine release, as well as the characteristics of the physical feeling of the pouch inside the mouth.

Importantly, while both nicotine pouches and cigarettes aim at providing a comparable nicotine experience, the adult user experience cannot be compared as the products work quite differently from one another and the absorption of nicotine is radically different. On the other hand, the lack of combustion and the nicotine delivery route contribute to the pouches' reduced risk profile compared to cigarettes. The population health impact of these products depends on their acceptance by adults who smoke, as was demonstrated in the Nordics in the case of snus and nicotine pouches.

The science on nicotine pouches

While these nicotine pouches are among the latest products to be added to our smoke-free product portfolio, there is already clear empirical evidence showing that oral products can have a strong potential to replace cigarettes for existing adult smokers and have a positive impact on public health. To support further assessments on these products, priority lists of toxicants have been developed by multiple authorities.*

The German Federal Institute for Risk Assessment (BfR) has conducted a health assessment of nicotine pouches, which included experimental research and a review of existing research. They wrote:

Keeping this model of risk minimisation in mind, switching from cigarettes to nicotine pouches could represent a reduction in health risks for a person who smokes. However, measures should be taken to avoid that use of nicotine pouches leads to a higher nicotine intake compared with other products on the market.

Chemistry data on nicotine pouches

In analytical chemistry studies thus far, nicotine pouches have generally been found to contain very low levels of almost all toxicants measured, with many falling below the limits of detection or quantification as showed by the recent BfR study, which sampled 44 products across a range of nicotine content from 1.79 mg to 47.5 mg. (For context, the maximum nicotine level set by the SIS and BSI industry standards is 20 mg, which is followed by the main manufacturers). In line with the low toxicant levels, nicotine pouches have also not been found to be mutagenic or genotoxic, in contrast to cigarette smoke

*Priority lists of toxicants include those developed by the United States Food and Drug Administration (FDA), the analytes from the GOTHIATEK® standard developed for Swedish snus, as well as the Swedish Institute for Standards (SIS) and the British Standard Institute (BSI).

Pharmacokinetics and pharmacodynamics on nicotine pouches

The BfR report mentioned above also included a review of research on the pharmacokinetics of nicotine in people who used nicotine pouches. The peak nicotine level (C_{max}) in the blood for users of oral nicotine pouches was in the range reached for a single cigarette for most products. The time to reach this peak (T_{max}) depended on the length of time the product was used, meaning that the peak nicotine level was reached soon after the product experience was ended.

The participants in these studies were current smokers, for example in one study by Rensch *et al.*, or dual users of oral smokeless products in other studies such as a study by Liu *et al.* Participants generally reported reduced urge to smoke after using nicotine pouches, and found the pouches to be acceptable, although less so than cigarettes as the participants were already used to.

Researchers investigated the biomarkers of exposure to toxicants in cigarette smoke, as well as biomarkers of potential harm, for nicotine pouch users compared to the levels measured in current, former, and never smokers. The study's results indicate that nicotine pouch users have significant improvements to both biomarkers of exposure and biomarkers of potential harm compared with smokers.

Actual use of nicotine pouches

A preprint study to explore actual use of nicotine pouches under ambulatory conditions was conducted over six weeks with adult smokers, smokeless tobacco users, and dual users of cigarettes and smokeless tobacco in the U.S. Nicotine pouches were supplied to participants *ad libitum*. Approximately 78% of the dual users replaced their smokeless tobacco use with nicotine pouches, and more than 80% of the same group reduced their cigarette consumption. 70% of smokeless tobacco users stopped consuming smokeless tobacco after six weeks' use of nicotine pouches. At the time of their enrollment, these participants also did not intend to quit smoking or using smokeless tobacco during the next 30 days, and so the results may be indicative of nicotine pouches' potential for harm reduction.

Unlike in the U.S., nicotine pouches are not yet broadly available in Europe. Still, there are similar trends in awareness of the pouches and generally low prevalence of use with Nordic countries being outliers. In the U.K., nicotine pouch use is most common among current smokers and recent former smokers, and dual use with e-cigarettes has also been noted.

PMI's research on nicotine pouches

Research on the category of oral tobacco and nicotine products helps people to understand the potential impact the category of products could have on public health. But it is also important to scientifically assess each product individually to learn what its risk profile is compared to cigarettes. We have conducted initial assessments of our nicotine pouches before their launch, and we have finalized several preclinical studies, as well as a nicotine pharmacokinetics study. Further assessment of these products is planned and underway.

Conclusions

To summarize: nicotine pouches are a promising smoke-free product in terms of harm reduction, and they offer smokers a different experience compared to cigarettes, heated tobacco, or e-cigarettes. Oral nicotine-containing products like these contribute to a portfolio of alternatives to cigarettes with a greater variety of options for current adult smokers who would otherwise continue to smoke. Now that they are a part of our smoke-free product portfolio, we look forward to continuing to assess these products' harm reduction potential.

MANUFACTURING THE TOBACCO STICKS

IN OUR TOBACCO HEATING SYSTEM AND OVEN HEATING SYSTEM

The tobacco sticks in our Tobacco Heating System (THS), which is commercialized as *IQOS*, and in our latest heated tobacco device, the Oven Heating System (OHS), are designed to heat tobacco to release a nicotine-containing aerosol for the user to inhale, but without burning the tobacco like a cigarette does. The THS and OHS heat tobacco to significantly lower temperatures, and, therefore, unlike cigarettes, produce no fire, ash, or smoke. Because the tobacco is heated and doesn't combust, these heated tobacco products (HTPs) emit 95% less harmful toxicants compared to cigarettes. However, this does not necessarily equal a 95% reduction in risk. The THS and OHS are not risk-free and provide nicotine, which is addictive. The "95% less" represents the average reduction in levels of harmful chemicals from relevant internationally recognized regulatory lists, compared to the smoke of a reference cigarette. Here, we examine how the tobacco sticks, also known as heated tobacco units (HTUs), are manufactured in our HTPs.

What's inside heated tobacco units?

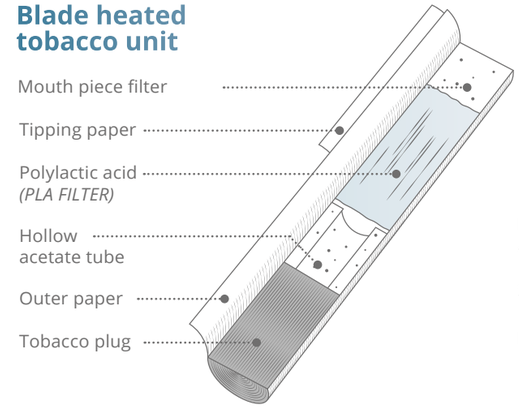
HTUs include a uniquely processed tobacco plug designed for heating, not burning, and a mouthpiece filter. Other elements may include outer and mouth-end papers, a hollow acetate tube, and a polymer-film filter, depending on the type of HTU.

Blade and induction heating technology

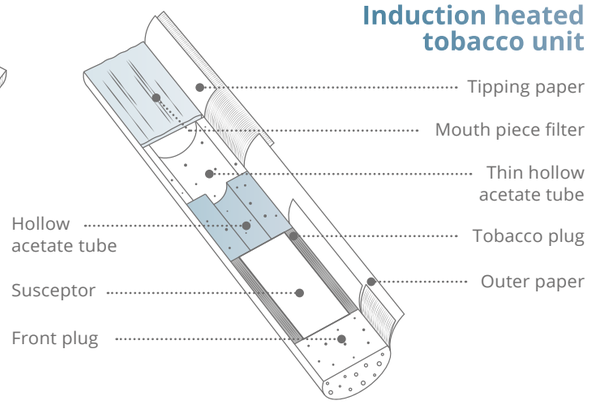
There are two heating technologies: blade and induction, used in our THS. Initial generations use blade heating technology and are designed to be used with specific HTUs, commonly known as *HEETS* or heatsticks. They rely on resistive heating, and contain an electronic system, which heats the tobacco within a precisely controlled temperature range to avoid burning it. This is achieved via a heating blade. The blade also functions as a temperature monitor, allowing the THS to control the temperature of the tobacco.

Our latest HTP, commercialized as *IQOS ILUMA*, uses induction to heat tobacco. There is no direct contact between the electronics and the heating element, a metal strip introduced at the center of the tobacco plug. When the specifically designed tobacco stick, called a *TEREA SMARTCORE STICK*™, is inside the holder and the system is turned on, an electric current flows through the coil in the holder. This current creates the magnetic field that heats the heating element inside the tobacco, which in turn heats the surrounding tobacco. In the manufacturing process, the main difference between the *HEETS* and *TEREA* HTUs is the insertion of the heating element in the tobacco plug inside the *TEREA* stick.

Blade heated tobacco unit

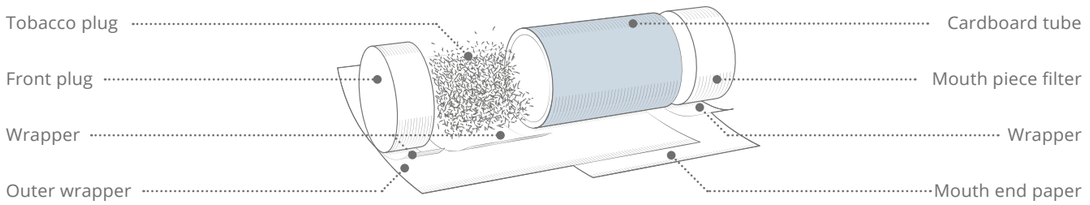


Induction heated tobacco unit



Resistive external heating with no blade

The OHS is commercialized as *BONDS* by *IQOS*. It uses resistive external heating, with no blade, via the ROUNDHEAT TOBACCO SYSTEM™, to heat the tobacco across the external surface of the tobacco stick instead of burning it like a cigarette does. These devices use specially designed HTUs called *BLENDS*. The HTUs contain specially processed tobacco for heating, a filter, a front plug, and a cardboard tube. The resistive heater is made of flexible polyimide, stainless steel tracks wrapped around a cylinder stainless steel tube, with an insulated thermal casing around it. The control electronics ensure the heater's temperature is controlled and provide protective monitoring to prevent overheating.



A closer look at the tobacco stick manufacturing process

The tobacco sticks are manufactured at specialized manufacturing centers. The dried tobacco leaves are processed in the Primary area of the centers, and the tobacco sticks are produced and packed in the Secondary area. The tobacco plug in the induction and blade HTUs is made from tobacco leaves, which are ground and reconstituted into tobacco sheets, called cast leaf. These sheets are then crimped and made into the tobacco stick rods. In the *BLENDS* HTUs, the tobacco plug is made from tobacco leaves cut into small pieces (cut filler) impregnated with glycerin. This processed tobacco is specifically formulated for heating and is not intended for smoking.

Tobacco sticks are made by blending high-quality tobacco from selected types and origins: Burley, Virginia, and Oriental. The next stage in the process is curing, which is the term used for drying tobacco, and is performed after harvesting the leaves from the field. Leaves are sorted by stalk position and quality, then packed in bales, which are evaluated by leaf buyers. Tobacco leaves then go through final processing, and the tobacco is dried, packed in cases, and shipped.

The best thing any adult smoker can do is to quit tobacco and nicotine altogether. However, the totality of the evidence available today from our rigorous scientific assessment program indicates that switching completely to our HTPs, while not risk-free, presents less risk of harm than continued smoking.

Cut filler process for OHS HTUs

The conditioning and casing application sprays water, steam, and glycerin on the tobacco leaves inside a rotary cylinder. The water and the steam soften and open the leaves, while the glycerin protects the tobacco from overheating and creates the aerosol when the tobacco stick is consumed. The leaves are then processed in the cutter machine to produce strips up to 1 mm in width. The strips are then dried at a high temperature to reach the right target of humidity.

After the drying process, additional ready-to-use tobacco components (like stems) are added to the lamina strips. Then, the flavor is sprayed on the product inside a rotary chamber to give the final taste to the substrate. Finally, the product is conveyed in a silo where it is blended to reach homogeneity. The final mix is called “cut filler” and is ready to be used in secondary processes.

Blending and grinding of tobacco leaves for induction and blade HTUs

The Blending and Grinding Line processes the tobacco leaves and transforms them into tobacco powder, which is used as a main ingredient in the cast leaf manufacturing. The tobacco powder is then mixed with four other ingredients - water, glycerin, fibers, and guar gum - to obtain a paste (slurry). Glycerin protects tobacco from overheating and creates a visual aerosol when the tobacco stick is consumed. Fibers create the tensile (strength) of the tobacco sheet, the tensile being the resistance when pulling on the cast leaf bobbin. Guar gum, a natural vegetable gum, binds all the elements together.

Cast leaf lines and bobbins for induction and blade HTUs

The slurry is cast on the steel belt with a blade at the beginning of the process, removing the excess slurry. Once the slurry has been sufficiently dried, the resulting tobacco sheet can be detached and placed onto a perforated belt. After the cast leaf comes out of the second drying zone, it is wound around a core to form a bobbin.

Crimping and tobacco rods for induction and blade HTUs

Crimping, the next step in the process, already exists in the paper making industry. The cast leaf is crimped to a specific profile while flavors are applied. Next, the cast leaf passes through a funnel and is glued to form a continuous rod. The rod will then be cut into tobacco sticks measuring 120 mm in length.

Polymer-film filter

The filter in the blade tobacco stick is used to cool down the aerosol to an acceptable temperature. It is made of polylactic acid (PLA), a biodegradable polymer-film, which is wrapped in a non-porous paper made of cellulose fibers. PLA is a thermoplastic aliphatic polyester obtained from corn starch, tapioca products (roots, chips, or starch), or sugarcane. It is used in several biomedical applications, as well as for food packaging. The induction and OHS tobacco sticks do not include the PLA filter. This section has been replaced by a chamber in which the aerosol condenses through fresh air intake. A plug has also been added at the end of the tobacco stick to ensure the heating chamber remains clean.

Packaging process

Finally, the double tobacco sticks are cut and turned to continue as single tobacco sticks to the packer. The single tobacco sticks are sorted and enveloped in paper. Two separate compartments are formed, and an inner frame is used to reinforce both compartments. The hinge lid then envelopes the 20 tobacco sticks to form the final pack.

Combiner

Once the rods are manufactured, they are moved to the combiner where they are cut to the expected length, and combined with the other components, such as the hollow acetate tube, cellulose-acetate mouthpiece filter, and outer and mouth-end papers. They are then wrapped and glued in the outer paper to form the tobacco stick.

CLINICAL STUDIES

Impact of switching from cigarette smoking to THS on systemic endothelial function in subjects with established atherosclerotic disease

The goal of this PMI clinical study is to demonstrate improvement in flow mediated dilation, a functional endpoint associated with the progression of atherosclerosis, when switching from cigarettes to the Tobacco Heating System (THS) in people with peripheral arterial disease and/or coronary artery disease. Atherosclerosis is thickening or hardening of the arteries caused by a buildup of plaque in the inner lining of an artery.

The study will also assess other cardiovascular (CV) functional endpoints, or cardiovascular biomarkers of potential harm representative of different pathophysiologic pathways associated with increased CV risk in smokers with established atherosclerosis. The three-group (cigarette, THS, smoking abstinence) 12-month study has an estimated enrollment of 1,816 participants.

It is expected that the totality of the evidence from this study will show the potential of THS to slow down the progression of atherosclerosis, thus helping to delay a CV event, or delaying a secondary event. The study is planned to be conducted in the U.S., Europe, and Asia, and has an estimated completion date of December 2025.

Effect of switching from cigarettes to THS on disease progression in mild to moderate COPD subjects with chronic bronchitis symptoms

The aim of this three-year PMI clinical study is to demonstrate the slowing of the disease progression including the improvement of Chronic Obstructive Pulmonary Disease (COPD) symptoms in smokers with mild to moderate COPD and a history of chronic bronchitis symptoms (sputum and cough) who switch to the Tobacco Heating System (THS), compared to those who continue to smoke cigarettes.

This study, which was announced in October 2022, will be a multiregional (Europe, U.S., and Asia) multi-center, open-label study with a three-group, parallel preference design (cigarette, THS use, and smoking abstinence). It will have an estimated enrollment of 1,895 participants and is expected to conclude in March 2026.

The study will be declared successful if a slowing of the disease progression is shown with the primary objective endpoint of forced expiratory volume in the first second (FEV1) post-bronchodilator at month 36 or if an improvement of COPD symptoms (COPD Assessment Test total score at interim analysis at month 12) is demonstrated.

Heated tobacco products and cardiovascular disease: A literature review

This literature review summarizes the results of *in vitro, in vivo*, and clinical studies that together demonstrate the cardiovascular disease (CVD) risk reduction potential of switching from cigarette smoking to scientifically substantiated smoke-free alternatives, such as our heated tobacco product, the Tobacco Heating System (THS).

Cigarette smoke contains toxicants that cross the alveolar barrier into the blood stream and elicit systemic oxidative stress and inflammatory responses, which can predispose smokers to the development and progression of atherosclerosis, leading to several types of CVDs, such as ischemic heart disease, peripheral artery disease, cerebrovascular disease, and aortic aneurysm.

The review cites several scientific studies that show the THS aerosol significantly reduces the effects on mechanisms that are causally linked to atherosclerotic plaque formation in human-derived *in vitro* systems, compared to cigarette smoke. Research also indicates switching from cigarette smoke to THS aerosol exposure causes reduced atherosclerotic plaque growth in an animal model of disease. The clinical data referenced in the review "clearly show that switching from cigarette smoking to THS use results in favourable changes in clinical risk endpoints, which shift in the same direction as they would upon smoking cessation", the authors noted.

While heated tobacco products are not risk free there is a growing body of research indicating that switching to these products represents a potentially less harmful alternative for adults who would otherwise continue smoking, the review concluded.

Reduction in exposure, inflammation, and oxidative stress after at least two years of switching to THS use compared to cigarette smoking

The objective of this PMI clinical study is to demonstrate beneficial effects of switching from cigarette smoking to Tobacco Heating System (THS) use for at least two years compared to cigarette smoking on both inflammation and oxidative stress status.

It also aims to show additional benefits on other mechanistic pathways along with inflammation and oxidative stress by the means of additional biomarkers of potential harm, and to assess association with functional benefits that are expected to be responsive to the extent of exposure to harmful and potentially harmful constituents.

This is a cross-sectional three-group study (cigarette smoking, THS use, smoking abstinence) with an estimated 960 participants enrolled and matched by region (Asia, Europe), age, sex, and average daily product consumption over the last two years as self-reported. It is expected to conclude in February 2024.

Reduced HPHC exposure in cigarette smokers switching to P4M3 Gen. 2.0 compared to continuing smoking, or smoking abstinence

This PMI clinical study aims to demonstrate the reduction of biomarkers of exposure to selected harmful and potentially harmful constituents (HPHC) in smokers switching from cigarettes to two flavor variants of P4M3, an Electronic Nicotine Delivery System (ENDS), compared to smokers continuing to smoke cigarettes for five days, or to smoking abstinence.

The data collected in this randomized, controlled, open-label, four-arm parallel group study in confinement will provide information on exposure reductions achievable in a well-controlled environment with full control on daily P4M3/cigarette consumption, and compared to smoking abstinence.

A reduction of exposure to HPHC from cigarette smoke is expected to diminish the health risk of nicotine consumption if switching completely to ENDS. The study enrolled 68 participants.

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 following pages include our product development and assessment efforts, our initiatives to share our methodologies and results, as well as independent research and government reports. More detailed information can be found at www.pmiscience.com.