

Inside the Cube

Introduction

Philip Morris International (PMI) is widely known as a cigarette company.

But in 2020, we issued our Statement of Purpose, reaffirming our 2016 commitment to deliver a smoke-free future.

We have focused on developing, scientifically substantiating, and responsibly commercializing smoke-free products that are less harmful than smoking, with the aim of completely replacing cigarettes as soon as possible. How do we make sure that we reach our goal? What are the efforts and investment needed to bring us closer to a smoke-free future?

Undoubtedly, bold visions call for bold moves. In order to achieve our ambitious goal, since 2008, we've invested more than USD 9 billion into the science and research of developing smoke-free products, and we employ more than 930 world-class scientists, engineers, and technicians to help us.

In 2009, PMI opened its research and development facility, thanks to its shape also known as “the

Cube,” on the shores of Lake Neuchatel in Switzerland (Fig. 1). Our company has invested USD 120 million to build this state-of-the-art facility, which was constructed in a way that conveys one word: transparency. Its transparent glass walls reflect the crystal-clear waters of the lake, and the thought behind the construction is aligned with the full scientific transparency that PMI stands for: We are transparent about all our scientific findings, we publish them online, and we invite fellow scientists to review and scrutinize them.

The Cube consists of three separate wings, named Earth, Wind, and Water, symbolizing the natural elements that surround it. It is no coincidence that one element—fire—is missing. We at Philip Morris International have made it clear that our goal is to achieve a smoke-free future, a future where tobacco combustion is just a memory.

When it comes to science and research, we set high standards for our work, and our scientific methods are inspired by the pharmaceutical industry. We share our scientific findings publicly and encourage others to review them. Our vision is to offer current adult smokers a better choice than continued smoking. How are we making this vision a reality? By developing a portfolio of smoke-free products that deliver nicotine without burning tobacco and that current adult smokers find satisfying. Let's have a closer look at how we approach science in the Cube (Fig. 2).

“Cube” staff

The 930 world-class scientists, engineers, and technicians work collaboratively in 30 disciplines (physics, biology, chemistry, medicine, epidemiology, clinical science, behavioral science—to name just a few), to create reduced-risk products that mimic the sensory components of cigarettes, but without the smoke.



Figure 1. Research and development facility “Cube”

OUR SCIENTIFIC APPROACH



PLATFORM DEVELOPMENT

The assessment of a smoke-free product's risk reduction potential relies on the quality of the initial product design and on strict manufacturing controls to ensure that the product delivers a consistent aerosol. The platforms are specifically designed with the aim to eliminate or reduce the levels of Harmful and Potentially Harmful Constituents (HPHCs) found in their aerosol compared to those found in cigarette smoke.

In this initial phase of designing a product, it is verified that the product's design does not pose any additional risks to the user. Only then can we begin to conduct further research.



TOXICOLOGICAL ASSESSMENT

Toxicological assessment aims to confirm whether the reduced formation of HPHCs leads to reduced toxicity and reduced risk of smoking-related diseases in laboratory models.

PMI conducts a series of *in vitro* and *in vivo* studies on smoke-free products, following Good Laboratory Practices (GLP), to determine whether the reduced levels of HPHCs lead to a reduced toxicity, compared with cigarette smoke.

We take toxicological assessment one step further by using a new area of science known as systems toxicology, which allows us to determine whether reduced toxicity leads to reduced risk of smoking-related diseases in laboratory models.



CLINICAL ASSESSMENT

Clinical studies are a cornerstone of our assessment program. They help determine the extent to which adult smokers would find the product an acceptable alternative to cigarettes.

And they also investigate whether switching from cigarettes to a smoke-free product has a beneficial effect on a smoker's health profile by reducing the risk of smoking-related diseases as compared to continued smoking.



PERCEPTION AND BEHAVIOR

For smoke-free products to have an overall positive impact on public health, it is important that non-smokers do not start using them, and that smokers who intend to quit are not dissuaded by these products.

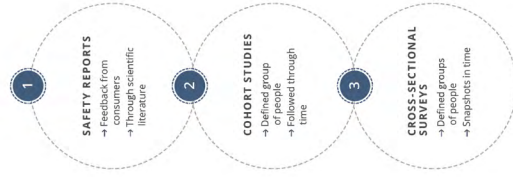
Moreover, smokers should understand that quitting is the best way to reduce smoking-related health risks, and that these products are only for smokers who would otherwise continue to smoke.



LONG-TERM ASSESSMENT

The assessment of our smoke-free products continues after the products are placed on the market.

Long-term assessment, including post-market studies, will confirm the safety of our products and reduce the risk of smoking-related diseases such as chronic obstructive pulmonary disease, cardiovascular disease and lung cancer.



Find out more about scientific researches in an interview with Nikolai Ivanov, a scientist at Philip Morris International and Lead of research technology department at the PMI's research and development center Cube.

1. What assessments were performed in the laboratory you lead?

In 2021, we have completed a dozen toxicological studies related to product assessment. The studies cover different variants of Heat-not-Burn products as well as electronic cigarette systems. They also involve different levels of complexity of the assessment process: *in vitro* cell culture, *in vivo* OECD studies in rodents and clinical studies. The latest innovative and state-of-the-art Systems Biology methods have been used to perform a comprehensive molecular analysis of the samples to ensure that we have investigated all potential biological effects. Our studies have confirmed the reduced exposure and reduced risk of the smoke-free products compared to the cigarettes. The rodent studies are performed in PMI Singapore facility and only if required by the regulatory authorities. Majority of studies consist of cell culture-based assays permitting to follow "Reduce, Replace and Refine" principles. All studies are conducted under our internal Quality Management System guidelines on qualified laboratory instruments. Key lab workflows are performed under Good Laboratory Practices (GLP) and Good Clinical Laboratory Practices (GCLP) guidelines and in May 2021 we have successfully passed the latest GLP inspection by Swiss authorities.

Figure 2. PMI scientific approach

2. How many tests are currently being done in your laboratory and to which areas do the tests you conducted relate?

We perform thousands of tests per year in the areas of Genomics, Transcriptomics, Proteomics and Metabolomics to evaluate the up- and downregulation of pathways and molecules potentially related to harmful compounds or smoking-related diseases.

3. When it comes to the trials that have been conducted so far, which ones are you most proud of, which would you point out and why?

There have been many complex and scientifically important studies. However, I think that a set of studies^{1,2} to assess our tobacco heating system (THS 2.2.), in different mice models of smoking-related diseases has made the most significant impact in the scientific and the regulatory community. For the first time the reduction of risk of cardiovascular disease, chronic obstructive pulmonary disease and lung cancer has been demonstrated over the life-long exposure to the novel Heat-not-Burn product in the animal model. All these studies have been submitted with the MRTP application to the US Food and Drug Administration (FDA) as well as other regulatory authorities around the world to substantiate the product's reduced risk potential.

4. How do you share the results you get during the examination with the scientific community? Do you perhaps participate in congresses or results in professional journals?

We are actively publishing the results of our studies related to smoke-free products in peer-reviewed journals and presenting at international scientific conferences. In addition, we regularly share our results and findings on the PMI Science website

¹ An 8-month systems toxicology inhalation/cessation study in Apoe^{-/-} mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with conventional cigarettes

² Respiratory Effects of Exposure to Aerosol From the Candidate Modified-Risk Tobacco Product THS 2.2 in an 18-Month Systems Toxicology Study With A/J Mice

(<https://www.pmiscience.com/library>). Our scientists are also members of numerous scientific associations and societies that encourage exchange and communication of the most cutting-edge research.

5. Are there any similarities with studies conducted by pharmaceutical companies?

Since in the United States both the pharmaceutical and tobacco products are regulated by the FDA, in design and execution of the studies we have been following guidelines very similar to pharma industry (including GLP, GCP, GCLP, etc.) as they have been developed and improved by the Center for Tobacco Products (CTP) at FDA. However, our MRTP application is probably the most comprehensive product assessment that has been submitted to the CTP FDA including all the chemistry, pre-clinical, systems toxicology, clinical and behavioral studies.

6. In July 2020, US Food and Drug Administration authorized PMI's leading heated tobacco product as a modified risk tobacco product (MRTP) with reduced exposure information. What does this decision mean for PMI and you personally?

The authorization of our leading heated tobacco as a modified risk tobacco product with reduced exposure information by the FDA means that the decade of our scientific efforts and work have been externally recognized by the most advanced regulatory agency in the world. I believe it was the most important milestone for all our PMI colleagues to date.

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