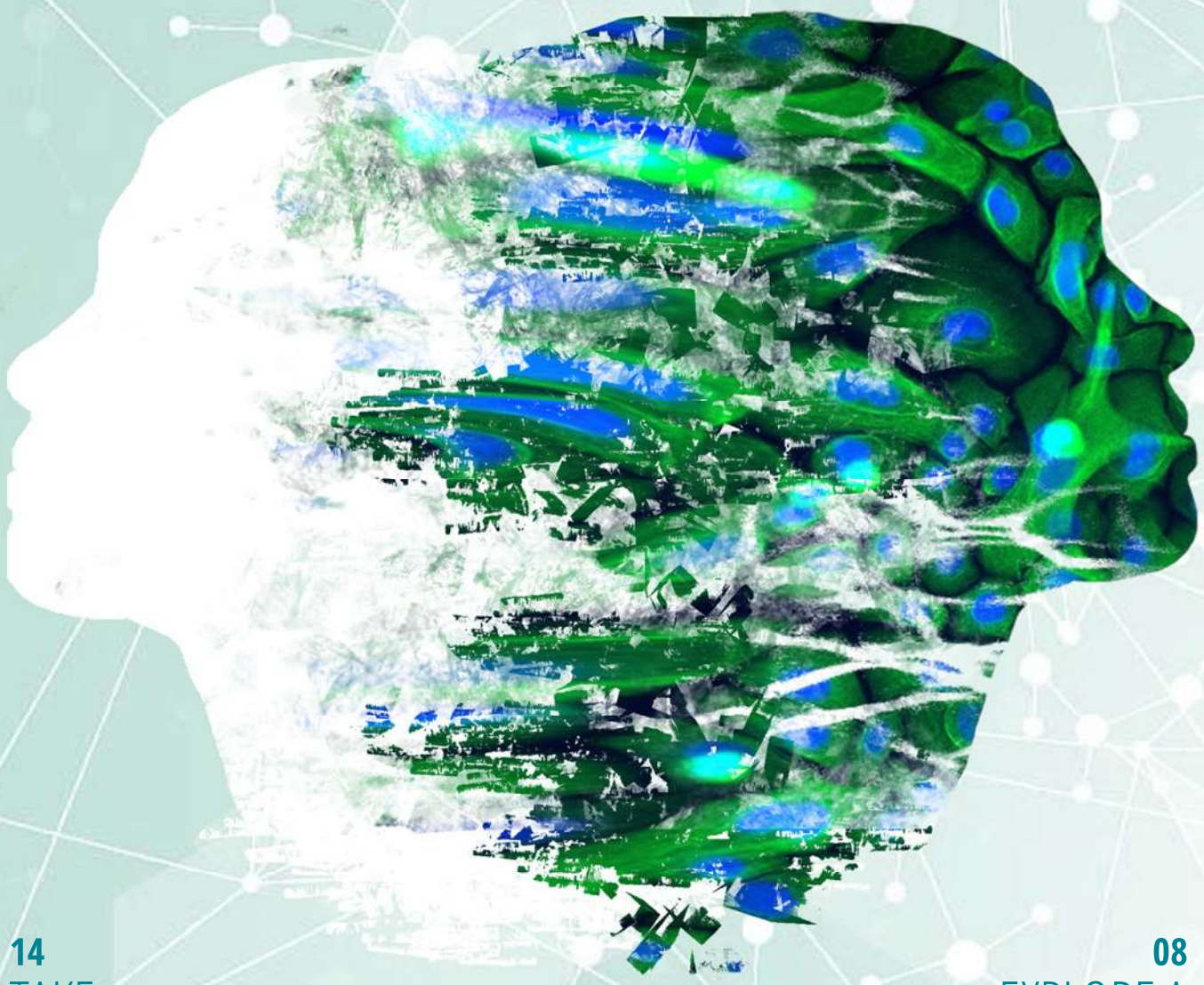
# SCIENTIFIC UPDATE

PMI SCIENCE – PHILIP MORRIS INTERNATIONAL

MAY 2021 | ISSUE 12

# THINKING AHEAD



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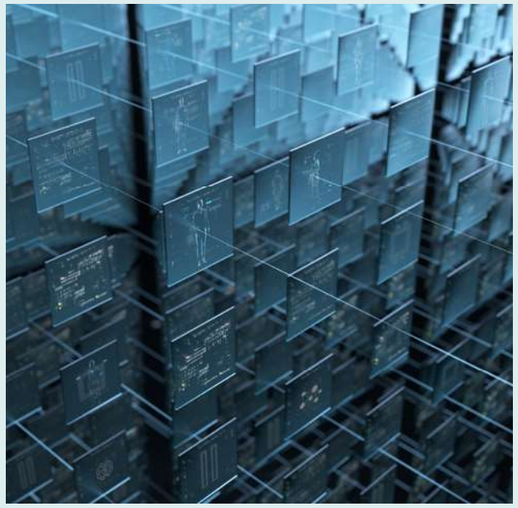

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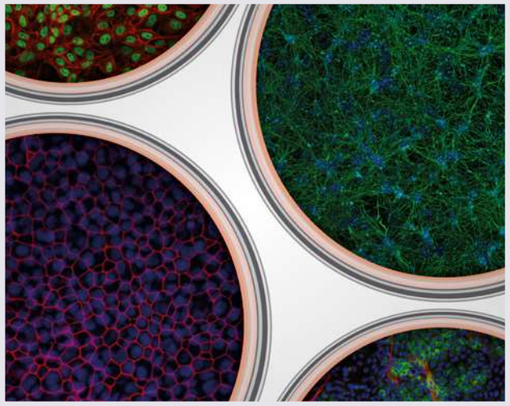

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**PMI Science looks back at 2020**
Stories, moments, and milestones from 2020




# INTRODUCTION

The past year, with ample time for introspection, was a year for people to think and make big decisions. Same for us at Philip Morris International.

In February this year, we announced new goals that complement continued efforts to realize our smoke-free vision: we are expanding to develop products that go beyond tobacco and nicotine. These efforts run in parallel to our continued work to encourage adult men and women who would otherwise continue to smoke to switch to smoke-free products, and phase out cigarettes completely.

In this issue of the Scientific Update, we recall our journey through 2020, examine the capabilities that our research on smoke-free products have given us, and discuss how we can apply those capabilities to develop new research initiatives and products.

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# THE FUTURE OF RESEARCH AT PMI

**Dr. Jorge Insuasty, Chief Life Sciences Officer, discusses what's on the horizon for research at PMI.**

PMI is transforming, in many senses of the word. We are transforming our industry, we are transforming our products, and we are transforming our business model. These transformations are evident in our smoke-free product portfolio, a range of products developed for adults who would otherwise continue to smoke cigarettes.

PMI's transformation debuted with a vision centered on phasing out cigarettes in favor of a portfolio of less harmful alternatives to smoking. That smoke-free portfolio has become, and continues to be, important for us from both a business and research perspective. We continue to research and develop scientifically substantiated, non-combustible, and less harmful alternatives to continued smoking, at the same time working to provide adult smokers' access to better products. Along the way, we've developed new and innovative assessment methods, and gained new expertise in device technologies that are useful across industries and applications.

With all that we've accomplished so far, there are some people who still don't believe that our transformation is real and ask: is a smoke-free future really the purpose we are working toward? Yes. Can smoke-free products really have the impact we think they can? Absolutely, the science speaks for itself. What happens when all smokers who won't quit have switched to smoke-free products? That's a great question, and one we are prepared to answer.

## PMI is moving beyond nicotine

PMI possesses significant expertise in product formulation, aerosol chemistry and physics, device technology, clinical research and best in class preclinical safety and inhalation models. All of these position us well to continue our transformation and emerge into new growth opportunities. There are mainly two areas we are looking at expanding our research efforts and growth.



The **first growth platform** is on respiratory drug delivery, where we can use our expertise in the delivery and scientific assessment of aerosols, as well as our experience in device technology for medical applications.

The **second growth platform** is to move into botanical products addressing benefit areas such as Energy, Sleep, Calm and Focus – again using our expertise in inhalation science and technologies but also plant substrates.


Respiratory delivery is in general a method of delivery that provides consumers and patients with well differentiated products and/or drugs. Many products in the wellness and drug sector, although demonstrating good efficacy, still leave open unmet medical and consumer needs. Two of those unmet needs pertain to the time until someone can feel the effect and the side effects (safety profile) of a given product; both are linked (at least partially) to the route of administration.

For example, when a product is taken orally it takes time for the expected effect to set in. Also, due to the dose needed to achieve the expected effect, side effects may occur. Inhalation as an alternative form of application can offer advantages in both areas due to the faster uptake of the active compound, the potentially lower dose necessary, and higher bioavailability of the active compound achievable compared to when a product is taken orally in the same dose range.

## First steps in a new direction

With PMI moving into these new business areas, we have now given the answer to the question - ***"What is next in PMI's transformation?"*** And we have set for ourselves a serious objective: at least USD 1 billion of our company's revenues will be derived from our new business areas by the year 2025. To reach this objective, we will:

**1)** rely on and expand upon our existing core capabilities,
**2)** seek partnerships with entrepreneurs and companies that have the proper experience and credibility in the relevant fields,
**3)** keep a strong focus on specific benefit and disease areas which we will announce more concretely in the future.



**$$$**

**≥USD 1 BILLION**

in revenue from beyond nicotine by 2025

**>50%**

of our net revenues to come from smoke-free products by 2025

**>40 MILLION**

smokers switch to our smoke-free products by 2025

## Our future business areas will complement a smoke-free future

Expanding into the areas of botanicals and respiratory drug delivery complements our current smoke-free future objectives for 2025, such as our goal of converting more than 40 million adult smokers to our smoke-free products when they would otherwise have continued to smoke cigarettes.

Expanding into these new product areas certainly gives us additional room to grow from a business perspective, but it also allows us to put many of our areas of research expertise to good use. Those research capabilities are going to carry us through this next step of our transformation.

We have always said that we wanted to truly change the industry – and now we are embarking ourselves into the next chapter of this journey.

## QUESTIONS &ANSWERS

### *Dr. Insuasty's perspectives on new initiatives*

**Why is PMI working on these new initiatives?**
Many researchers in the field of harm reduction have asked us why we are not using our knowledge in aerosolization and inhalable devices beyond the tobacco harm reduction space. We believe that this was the right question to ask, and building upon the research expertise and knowledge we've gained from developing and assessing smoke-free products, we are in a really good position to work on, for example, respiratory drug delivery.

This method of delivering a drug is not as well developed as taking a pill or drinking a syrup. But respiratory delivery can become important for society because it has advantages over the traditional medication delivery methods. Medicines delivered via the respiratory tract allow a rapid onset of the drug effect and potentially reduce side effects due to the lower dose that might be needed for example compared to taking a pill. Similar for botanicals: we know how to work with plant substrates. We also know how to aerosolize and assess these kinds of products. In short, we are leveraging the areas where we have strong research and technology expertise to strengthen our business while making a difference for society.

**Is now the right time to introduce these new directions?**
There's no time like the present to plan for the future. We have a lot to offer in these new areas, and it would be inconsistent with our scientific mission not to use our knowledge and embark into new business areas.

**With all these new initiatives, are you still serious about transitioning to smoke-free future?**
Absolutely. We're committed to work toward phasing out cigarettes completely, what we call our smoke-free future. We have expressed the goal of reaching more than 50% of our net revenues by 2025 from smoke-free products. That really speaks for itself, but then we also have our goals of switching over 40 million adult smokers to our smoke-free products. And then we even have shared with the investor community our ambition to achieve by 2025 at least USD 1 billion in revenue from beyond nicotine products. Those goals, and the progress we've made so far, only makes sense if we're serious about a smoke-free future. And we are.

# A smoke-free future **AND BEYOND**

**At PMI, we have developed a rigorous scientific assessment program to assess our smoke-free products. In the process, we've developed skills, facilities, and experience that we can apply to a wider range of research questions.**

PMI has **invested over USD 8.1 billion since 2008** in our fundamental research, product development, scientific substantiation, and manufacturing capacity of our smoke-free products. **USD 120 million went into the construction of our R&D facility, the Cube,** in Neuchâtel, Switzerland. And our investments don't stop there. We also invest in our people: **more than 430 men and women who are world-class scientists, engineers, and R&D experts.**

Our researchers have published images of solid particles from cigarette smoke as small as tens of nanometers, and they've measured nanograms of chemicals. They've collected terabytes of data, for which our scientists have developed high performance computing infrastructure to store and analyze that data. And, with 984 randomized participants enrolled in the 6-month study, they've conducted what is likely still the largest study of its kind to date on the topic of tobacco. We've even published a book on the toxicological evaluation of electronic nicotine delivery products.

In short, PMI has an outstanding research facility and excellent capabilities across a range of scientific fields. So why wouldn't we put those facilities and capabilities to good use?

We already apply ourselves to our smoke-free product research and assessment, working to transition away from cigarettes and toward smoke-free products.* That's what the Cube was built for. But we also do much more than that, contributing more broadly to the fields of research in which we work.

Here are a few examples of the research PMI currently conducts, both alone and in collaboration with other researchers, and an explanation of how that work could also impact research beyond smoke-free products.

**8.1 BILLION USD**
invested in research

**120 MILLION USD**
construction of the Cube

**430 MEN AND WOMEN**
scientists, engineers, R&D experts



## Understanding the airway

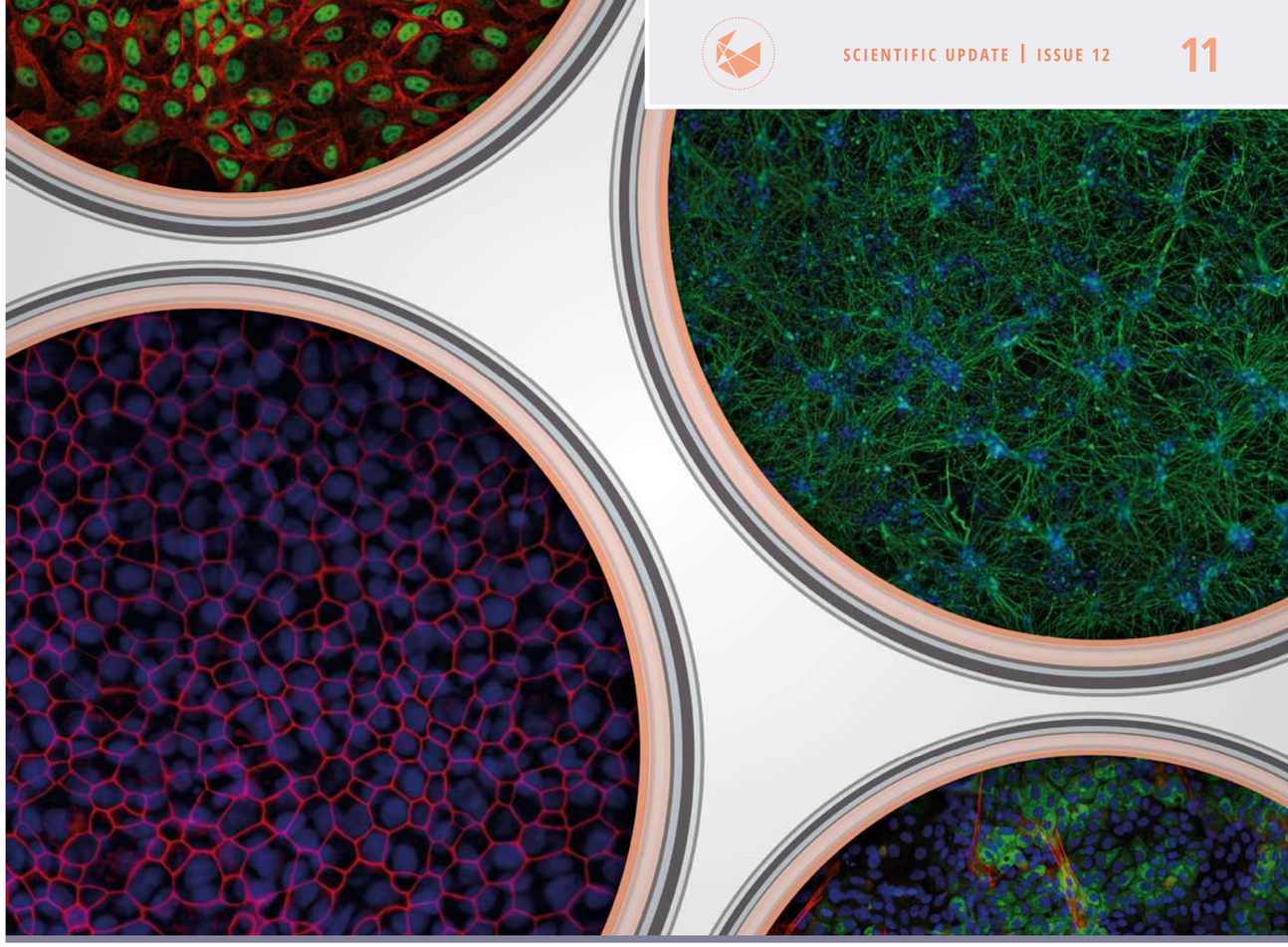
Considering the fact that smoke-free product aerosols are inhaled into the lungs, it is no surprise that our scientists are experts at modeling and understanding interactions between aerosols and the human airway — the path through which air reaches the lungs. This research is clearly important to understanding our smoke-free products, but it can also be informative for scientists working on inhalable therapeutics.

In February of 2020, we were part of a team that published the research showing how models of the airway can be personalized to an individual's unique airway shape. Age, gender, weight, fitness, health, and disease status can all impact the shape and functioning of an individual's airway. This publication details a model that can be used for person-specific simulations of how air is breathed in, gases are exchanged, and an aerosol is deposited along the airway. Information like this could help scientists who are working on therapeutics better understand how pharmaceuticals are delivered into the body, their efficacy, and determine or predict possible adverse effects before they happen.

More recently, PMI scientists were part of a collaboration to develop three-dimensional organotypic cell cultures of the human lung from multiple donors, creating a cell culture with approximately the shape and function of real human lung tissue. These cell cultures varied from donor to donor in their shape and their response to stimulation, but they were able to work and metabolize similarly.

Building on these avenues of research, PMI scientists have sought to develop a new system that can simulate exposure to various inhaled substances. The independent holistic air-liquid exposure system (InHALES) simulates the human airway in both shape and function, delivering aerosol doses to cell cultures. The system, like the human respiratory tract, can actively breathe, operate medical inhalers, or take puffs from tobacco products.





## Advancing toxicology methods

PMI is at the forefront of systems toxicology, using systems biology and applying it to toxicology. This branch of science aims to quantitatively understand, model, and predict the response of cells to external stimuli and can be expanded to assess systems and organs. In our product assessment, we use systems toxicology to build a detailed understanding of the mechanisms driving the biological response to toxicant exposure. This approach and these methods can be used to assess the risks of chemicals, drugs, and consumer products.

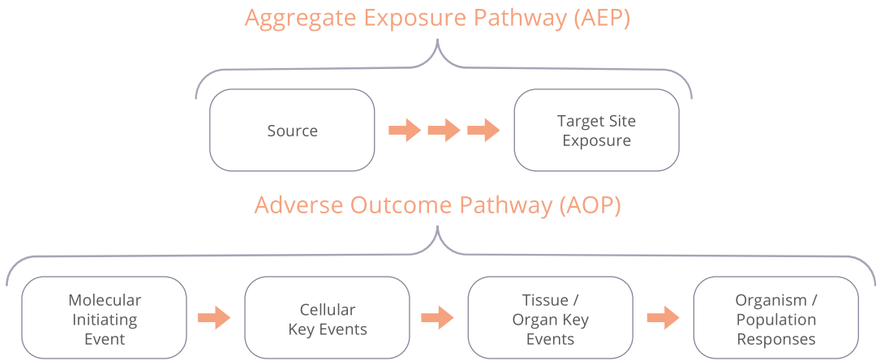
Predicting the impacts of the exposure to a new compound is a fundamental challenge in biomedicine that systems toxicology can help with. This prediction means identifying both the intended and non-intended effects of the compound. In one review, we explain why systems toxicology is a powerful approach to predict the likelihood of undesired drug effects and begin to outline the mechanisms leading to these effects. In systems toxicology, scientists combine the power of technologies that allow rapid aggregation of large quantities of data with advanced computational approaches that use complex network models with standard endpoints from preclinical and clinical studies. Doing this allows for a system-wide evaluation of the effects a drug can have on the biological system.

The effects of drugs and chemicals on the system can be measured through biomarkers, which are chemicals or other signals in the body that can indicate something about the body's response. For example, exposure to a chemical or drug, development of a disease, or how far along a given disease might be. These could all be quantified to some extent based on biomarker measurement.

Biomarkers can be especially important for detecting and monitoring the progression of many diseases. Because many of the available biomarkers are often not specific enough, better biomarkers are needed to improve disease risk assessment and monitoring. In this review, we discuss research findings on lipid biomarkers and the possible connection between these biomarkers and cardiovascular disease, chronic obstructive pulmonary disease, and aging. We also stress the need for improved quantification, method standardization, and establishing reference values to more efficiently translate research findings into the clinical practice so that newly identified biomarkers can be put to practical use.

## Establishing a pathway from exposure to response

***An AOP begins when the exposure initiates the first event in the pathway. An AOP contains one or more key events inside the body, and ultimately results in the organism level or population level response.***




## Reducing animal studies in research

Organ-on-a-chip technologies, also called microphysiological systems, represent promising tools to advance patient benefit and reduce animal testing, because they can mimic the human biology *in vitro* by allowing multiple "organs" to work together. But there are still many hurdles to their wide use in industry and acceptance by regulators. A team of 46 experts, including PMI scientists, worked together to analyze the current life-cycle of organ-on-a-chip-based assays. In the resulting extensive report, the authors give recommendations and a roadmap towards regulatory acceptance of models based on organs-on-a-chip systems. Such regulatory acceptance would be to the patients' benefit and would reduce the use of laboratory animals in the drug development process.

Scientists can also minimize the use of animals in research when they have a good understanding of the mechanisms that lead to disease or a negative reaction to a chemical. Adverse Outcome Pathways (AOPs) describe a series of biological events that lead to adverse or undesired effects. Developing AOPs can help identify and address gaps in our understanding of disease development or chemical exposure. This lets scientists identify key events involved in causing toxicity and then optimize non-animal approaches that can be used to investigate them.

In a 2016 workshop attended by government agencies, industry, academics, and non-governmental organizations, experts developed a strategy to establish confidence in non-animal approaches for the assessment of acute inhalation toxicity. This 2018 paper details the outcome of that workshop. It describes the AOPs and the toolbox of *in vitro* and *in silico* models that can be used to assess the causal chain of events leading to toxicity following inhalation exposure. As part of the workshop, the participants developed a decision tree to guide scientists toward designing their studies with strategic consideration to minimize animal use where possible. This decision tree can also facilitate standardization of non-animal testing approaches.

***An artist's rendering of the human bronchial cells used in a lung/liver-on-a-chip device. Such devices represent promising tools to reduce animal testing.***



## Pitching in during a pandemic

Like many people around the world, our researchers spent time in spring 2020 contemplating the question: What can I do to help my neighbors during a global pandemic? Our researchers came up with many ways to help, and they continue to generate new initiatives that make a difference.

As many people experienced around the beginning of March 2020, there was a hand sanitizer shortage. That was the case in Neuchâtel, the location of our research facility, the Cube. On Thursday, 19th of March 2020, Switzerland's federal office of public health, the FOPH, suspended the requirement for authorization to produce alcohol-based disinfectant so that it could be made more readily, in response to the crisis. One day after the requirement was lifted, PMI scientists had produced 450 bottles, all with labeling in accordance with national guidelines. The next Monday, we were already delivering the bottles to cantonal authorities.

In two months, 400 liters of hand sanitizer were produced in the Cube, 300 liters of which were donated to cantonal authorities for hospitals, to homes, and to the Neuchâtel Center of Psychiatry (Centre Neuchâtelois de Psychiatrie). Cube scientists also advised our colleagues in PMI factories around the world how to make the hand sanitizer, resulting in tens of thousands of bottles donated globally.

PMI scientists have also assisted local efforts to combat COVID-19 by supporting testing efforts beginning in March 2020. As part of multiple collaborations with area hospitals, PMI scientists have developed sensitive test methods for the virus, performed and collected nasopharyngeal swab collection and also rapid antigen tests, and analyzed hundreds of test samples.

## A lasting positive impact

Whether they are conducting research on our smoke-free products or branching out to other topics like new initiatives such as botanicals or respiratory drug delivery, our researchers apply state-of-the-art methods and standards for study development, data collection, and analysis. As is often the case in science, the approaches we've used and results we've collected along the path of our assessment program can be useful to researchers beyond the tobacco industry. Our scientists are proud to be working toward delivering a smoke-free future, and by now it's clear that their work can have an even broader positive impact through the sharing of our science. That's an opportunity we're not willing to pass up.

**** Smoke-free products are not risk free and contain nicotine which is addictive.***

# PMI SCIENCE **LOOKS BACK AT 2020**

**As we work our way through a new year, we look back and remember the stories, moments, and milestones from 2020 to prepare for what's to come in 2021. We're predicting a continued trend within the scientific community of increasing transparency, collaboration, and science-based decision-making.**

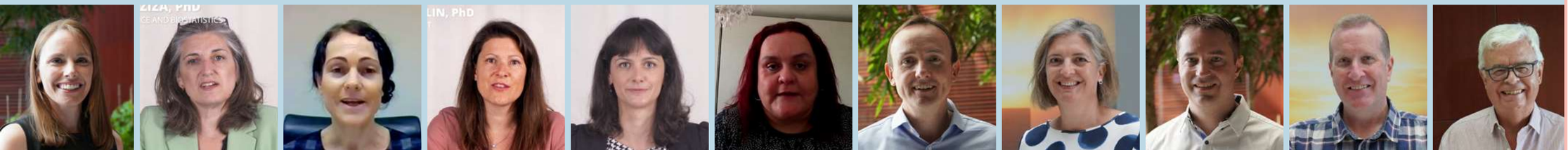
## Social distancing has brought scientists around the world together

The scientific community really felt like a community in 2020, as scientists around the world have been working behind the scenes on invaluable projects while collaborating at a distance. As the public turned to scientists for credible information and solutions related to the COVID-19 pandemic, we saw a wave of researchers from nearly all disciplines drop what they were doing to learn more about how to combat the virus. We saw firsthand how scientific publishers released free special issues to keep the public up to date on current COVID-19 findings. More and more science-based discussions can be seen on social media, and it's easy to see the public's appetite for facts in real-time and open dialogue about public health. Since March, scientists have also been participating in new pandemic-related webinars like those hosted by the American Chemical Society, the British Society for Immunology, and the Association for Biosafety and Biosecurity. And crowdsourcing coronavirus research has expanded the concept of "scientific community" to include anyone with a computer who wants to help.

Over the summer, we interviewed our scientists to hear their stories about how the lockdown impacted their work, their colleagues, and their daily life. Manuel Peitsch, Chief Scientific Officer, talked about the different initiatives launched during the lockdown in response to community needs and how his team demonstrated fantastic spirit and entrepreneurship for creating new channels for collaboration. We also discussed with Catherine Goujon, Manager Chemistry Research, how COVID-19 forced us to innovate how we work and interact with one another.

Many of our colleagues also donated their personal time sewing face masks or 3D-printing face shields. It has been inspiring to see the community come together. It might be mostly at a distance, but always in the spirit of collaboration.

***"Everyone is doing something, even if doing something quite literally means doing nothing other than staying at home and following social distancing guidelines to help protect our communities."*** *– Dr. Moira Gilchrist*



## PMI Science brings its research transparency online

Scientific transparency is essential to progress. Conferences have always been one of our best tools to share our findings and open a dialogue with the scientific community. As restrictions on travel and social distancing have become commonplace, scientists have migrated their presentations and conversations online, adopting a virtual format. For some, in-person conferences used to present financial, travel, and time constraints. This transition to online settings helped lift some of these barriers. Conferences going virtual have increased inclusivity and broadened communications by reaching out to a wider audience and reducing the costs of attendance.

We were gearing up to attend one of our most important conferences in June 2020, looking forward to sharing our latest research with our stakeholders, when conference organizers were forced to shift the conference online in the interest of safety. In the process, they had to drop the scientific poster presentation sessions for logistical reasons, but we were still eager to share our latest research. So, we created a new way for us to share our research openly. That's the origin story for Open Science, a virtual conference to bring forward our findings to the public and have an open dialogue with the scientific community in the form of a live Q&A.

This first webinar was led by Dr. Gizelle Baker, VP Global Scientific Engagement, and she introduced five pre-recorded presentations by our scientists. The topics explored the fundamental research and scientific evidence behind our smoke-free products. We dove into the risk assessments and the effects of switching to our leading heated tobacco product. The one-hour webinar was hosted three times throughout the day to accommodate multiple time zones. Over 1,000 participants registered for the event from 50 countries. After the presentations, Dr. Baker and other scientists joined to answer live questions from the audience.

## QUESTIONS & ANSWERS FROM OPEN SCIENCE

***Do you develop any smoke-free products without nicotine?***

We are developing a range of smoke-free products and currently they all contain nicotine. We know that nicotine is one of the key elements that people smoke for, and therefore if we want to get people to completely stop smoking cigarettes and switch to these products, then products that contain nicotine may replicate more of the ritual and social experience that together form the reasons why people continue to smoke.

Therefore, products that contain nicotine can help maximize the number of people who completely stop smoking altogether and switch to these products. Therefore, currently we do not have any products in our development portfolio that do not contain nicotine.

## Dr. Gilchrist presents at GFN

The Global Forum on Nicotine (GFN) 2020 welcomed Dr. Moira Gilchrist, VP Strategic & Scientific Communications, to speak on the topic of the company's transformation from cigarettes to smoke-free products. The pandemic and social distancing made having a normal face-to-face conference impossible, and since the organizers decided it is a crucial time in nicotine science, policy, and tobacco harm reduction, they went virtual instead of canceling.

The theme was 'Nicotine: science, ethics, and human rights'. Presenters and hosts discussed developments in nicotine research, ethical arguments in favor of tobacco harm reduction, and human rights concerns.

In her session, Dr. Gilchrist presented the company's ambition to have 40 million of our cigarette smokers switch to smoke-free products by 2025 and our commitment to a smoke-free future. She discussed how science and technology help the industry deliver better products — presenting not only our findings but also independent studies supporting the case for scientifically substantiated smoke-free products. PMI's commitment to the cause was also highlighted by Dr. Gilchrist, as she described PMI's investment of more than USD 7.2 billion (now USD 8.1 billion) since 2008 in fundamental research, product development, scientific substantiation, and manufacturing capacity for better alternatives for adult smokers who would otherwise continue to smoke.

## A historic decision is made

On July 7th, 2020, the U.S. Food and Drug Administration (FDA) authorized the marketing of the *IQOS* tobacco heating system as a modified risk tobacco product (MRTP) with reduced exposure information. It's the first and, so far, the only electronic nicotine product to receive such authorization. In doing so, the agency found that the issuance of the modified risk tobacco product orders with reduced exposure information would be "appropriate to promote the public health and is expected to benefit the health of the population as a whole."

The decision clearly differentiates our leading heated tobacco product from combusted cigarettes and allows American men and women who don't quit to receive information about a product that is a better choice than continuing to smoke cigarettes. This is just the latest step in a regulatory process that started in December 2016, when the FDA received our MRTP application, and it continues toward the future as we participate in the order renewal process or seek authorization for reduced risk or harm communications.

The September issue of our Scientific Update explored this authorization in depth, including the timeline of the review process, the evidence behind reduced exposure, and how this authorization is an ongoing process.

## Available evidence to-date:

**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.



## Open Science presents the difference between smoke and aerosol

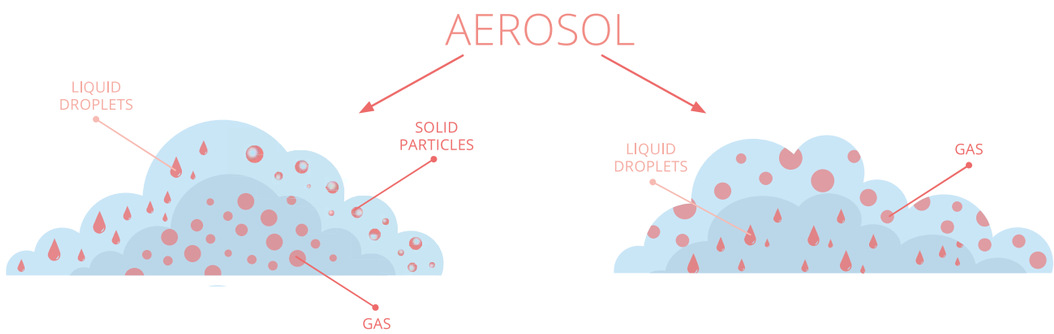
Also in September, we went back to basics by exploring the fundamental differences between cigarette smoke and heated tobacco aerosol as part of Open Science presentation series. Unlike our first Open Science webinar, in which our researchers presented posters of their latest research on multiple different topics, this time, the presentations followed a common theme.

One of the biggest problems with cigarettes is the burning of tobacco, which creates cigarette smoke and generates high levels of harmful chemicals. By heating instead of burning tobacco, we can avoid creating smoke and thus produce fewer and lower average levels of harmful chemicals. All five presentations addressed this fact from different perspectives.

Our scientists walked the audience through questions such as "What are the differences between smoke and aerosol?" and "Why is the absence of combustion so important?". Dr. Gizelle Baker hosted three sessions with pre-recorded presentations. Each session had its own live Q&A.

## They are both aerosols, but the differences are significant

An aerosol is a mixture of solid particles and/or liquid droplets in air or another gas.
Some examples of aerosols are smoke, smog, deodorant spray, clouds.
Even when you sneeze you create an aerosol.




### In cigarettes...

Smoke contains solid particles and liquid droplets therefore is an aerosol. It is a highly toxic mixture that contains thousands of chemicals as well as carbon-based solid particles formed when combustion occurs.

*But not all aerosols are smoke*

### In Heated Tobacco Products...

Heated tobacco products generate an aerosol containing liquid droplets and gas. It is not smoke as there is no combustion.

## QUESTIONS & ANSWERS FROM OPEN SCIENCE

***As the aerosol from Platform 1 is not smoke, does that mean that the aerosol is similar to the aerosol from e-cigarettes?***

The fact is that both Platform 1, our leading heated tobacco product, and e-cigarettes emit aerosols that are both generated in the absence of combustion. These aerosols are not smoke, as there is no combustion. Aerosol droplets are instead formed from the vapors of the aerosol former, which is glycerol, that is evaporated from the tobacco during the heating. When the vapor of this aerosol former later cools down, it condenses to form liquid droplets.

The very same process of vaporization and condensation happens in e-vapor products. There are aerosol formers in the e-liquid: propylene glycol and glycerol. Both are vaporized when the liquid is heated by the heating element. In the same way as for heated tobacco products, these vapors form an aerosol when they cool down and condense into liquid droplets. Both of the aerosols are liquid-based aerosol, containing fewer and lower levels of harmful and potentially harmful constituents compared to the smoke from combusted products, which contain thousands of chemicals and solid particles because it is the combustion that generates these solid particles.

# PMI SCIENCE

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## 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.