PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

SCIENTIFIC UPDATE FOR SMOKE-FREE PRODUCTS

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Issue 01 can be found here
Issue 02 can be found here

This Scientific Update explains **the science behind PMI's approach for achieving a smoke-free future** through a range of alternatives to cigarettes which do not burn tobacco.

The following pages include our **product development and assessment efforts, as well as our activities for sharing** our methodologies and results.

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

P.04

RECENT MILESTONES IN PMI'S RESEARCH

FOCUS ON: PMI'S MODIFIED RISK TOBACCO PRODUCT APPLICATION FOR ITS ELECTRONICALLY HEATED TOBACCO PRODUCT (EHTP)

WHAT'S INSIDE?

INTRODUCTION

"I have dedicated my career to pushing the boundaries of what we can learn about the molecular mechanisms of disease."

Before joining PMI, I spent 15 years working on the latest developments in computational and experimental methods at leading pharmaceutical companies. I am one of a community of over 300 scientists at PMI focused on developing better alternatives to cigarettes. Many like myself have extensive experience outside the tobacco industry.

There is a clear passion among all of us to tackle one of public health's major challenges – reducing the harm from smoking. Many of the scientists at PMI who were initially skeptical, including myself, are convinced by the clear commitment of the company to this objective.

Our mission requires a solid scientific foundation to demonstrate that less harmful products can exist. This requires that we conduct excellent science while adhering to the highest quality standards and that we transparently share our study results.

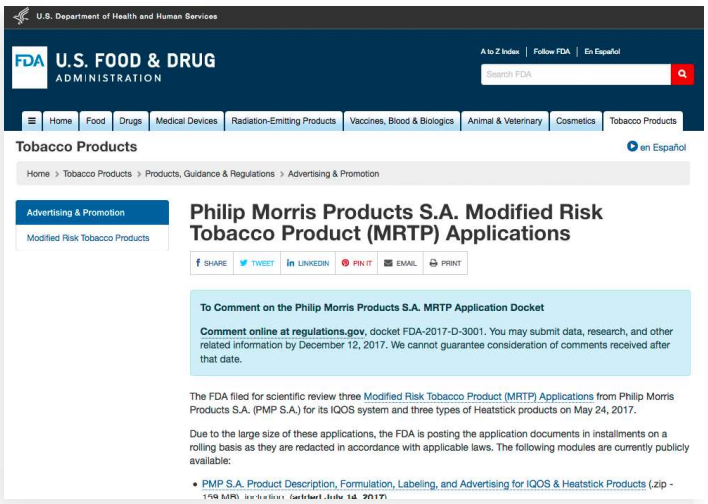
We were recently very encouraged by developments in the UK, US and New Zealand, all acknowledging the role that scientifically substantiated reduced-risk products can have for public health. The UK Department of Health's recently issued tobacco plan states that one pillar of its effort to dramatically reduce smoking is "*by permitting innovative technologies that minimise the risk of harm*" and to "*maximise the availability of safer alternatives to smoking*."

The US FDA Commissioner on July 28, 2017, announced a comprehensive tobacco plan, including a broad policy change designed to encourage the development of less harmful alternatives. Of particular note was his recognition that "*it is the other chemical compounds in tobacco and in the smoke created by setting the tobacco on fire that directly cause illness and death*" and that "*innovation can lead to less harmful products*" and play a role for public health.

We are focused on contributing to this effort.

We have applied to the FDA to market an innovative product that eliminates smoke by heating, rather than burning, tobacco. Our extensive research on this product shows that eliminating smoke reduces a smoker's exposure to harmful compounds and can potentially present less risk of harm than continued smoking. The application for our electronically heated tobacco product (EHTP)[1] is now public on the FDA's website, and we encourage those interested to review our methodologies and data.[2] We are dedicating this issue of our Scientific Update to our recent FDA application, explaining each step of our assessment program and their associated results.

Figure 1. Screenshot of PMI's submitted application for its EHTP on the US government website for public comment.



Beyond the 34 peer-reviewed publications that we have published to date on our EHTP, we also believe that science advances through scrutiny, and we welcome research from other institutions.

If you have any comments, we would like to hear from you. You can reach us through the channels at the back.

Prof. Manuel C. Peitsch
Chief Scientific Officer

REFERENCES

1 Also known as the Tobacco Heating Systems (THS)

2 https://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm546281.htm

ASSESSMENT PROGRESS OF OUR PRODUCT PORTFOLIO

HEATED TOBACCO PRODUCTS

One approach to significantly reduce the levels of toxicants generated and inhaled is to heat tobacco to a temperature below 400°C, below which combustion does not occur. From a smoker acceptance standpoint, these products have the advantage of more closely approximating the taste, sensory satisfaction and ritual they are used to with cigarettes.

PRODUCTS WITHOUT TOBACCO

Another approach is to produce an aerosol without the use of tobacco. The ability to precisely design the composition of the originating substance leads to better control of the resulting aerosol. These platforms may be best suited for smokers who are not necessarily looking for the taste and sensory experience of tobacco or are already using e-vapor products.

PLATFORM 1*

ELECTRICALLY HEATED TOBACCO PRODUCT (EHTP, REFERRED TO AS TOBACCO HEATING SYSTEM (THS) IN RESEARCH)

DESCRIPTION:
An electronically controlled heating blade precisely heats a specially designed tobacco unit to temperatures below 350°C. The experience lasts six minutes or 14 puffs, similar to that of a cigarette.

ASSESSMENT PROGRESS:
Our studies on EHTP, which include a large number of non-clinical and clinical studies, are very advanced and point in the direction of risk reduction and the potential to improve public health (see page 4).[3] An exposure response study designed to measure clinical risk markers when adult smokers switch to EHTP over a 12-month period is currently underway. Our post market program has been launched, with two observational studies underway in Japan with encouraging preliminary results.

PLATFORM 2

CARBON-HEATED TOBACCO PRODUCT (CHTP)

DESCRIPTION:
A carbon tip heat source precisely heats tobacco to a similar temperature to EHTP. The heat source is fully separated from the tobacco by a proprietary design.

ASSESSMENT PROGRESS:
Our non-clinical and early clinical studies are progressing well and show comparable results to EHTP, including a five-day human reduced exposure study. The clinical phase of a three-month reduced exposure study has been completed, with results expected by year-end.

PLATFORM 3

E-VAPOR PRODUCT USING NICOTINE SALT

DESCRIPTION:
Comprises products in which nicotine (a weak base) reacts with a weak organic acid to generate a respirable nicotine salt. We are exploring two routes for this platform, one with electronics and one without.

ASSESSMENT PROGRESS:
Our non-clinical studies for the electronic version are progressing well, and we have completed a clinical study showing a comparable nicotine profile to cigarettes.[4] A six-month clinical study will begin by year-end.

PLATFORM 4

E-VAPOR PRODUCTS (COMMERCIALIZED UNDER VARIOUS TRADEMARKS)

DESCRIPTION:
Battery-powered devices that vaporize a liquid nicotine solution (also known as e-cigarettes). Includes our new technology, *MESH*, designed to improve aspects such as product quality and consistency.

ASSESSMENT PROGRESS:
The non-clinical assessment on our e-liquids is well advanced.[5,6,7] For our *MESH* device, we expect the final report from a pharmacokinetic clinical study by early 2018. An indoor air quality study on our e-vapor products demonstrates no negative impact on air quality.

OTHER DEVELOPMENTS

We continue to search for new technologies in the smoke-free product space. PMI's venture fund invests in entrepreneurs and growth companies with new solutions for products that have the potential to present less risk of harm than continued smoking.
Our Idea Submission Portal offers innovators an opportunity to provide technical solutions that can enhance our product portfolio.

REFERENCES

3 https://www.pmiscience.com/library/pmi-science-ths-executive-summary

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5 Iskandar AR, Gonzalez-Suarez I, Majeed S, Marescotti D, Sewer A, Xiang Y, Leroy P, Guedj E, Mathis C, Schaller J-P, Vanscheeuwijck P, Frentzel S, Martin F, Ivanov NV, Peitsch MC and Hoeng J (2016) A Framework for *in vitro* systems toxicology assessment of e-liquids. Toxicology Mechanisms and Methods, 26:389-413. (PMID: 27117495).

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*See following page for detailed description.
The products depicted are subject to ongoing development, and therefore the visuals are illustrative and do not necessarily represent the latest stages of product development.

RECENT MILESTONES IN PMI'S RESEARCH

Focus on: Modified Risk Tobacco Product Application for EHTP

EXPLAINING THE MRTP PATHWAY

In 2009, the United States passed the Family Smoking Prevention and Tobacco Control Act, creating the world's first dedicated pathway for manufacturers seeking to make reduced-risk or reduced-exposure claims in comparison with another tobacco product. Referred to in the law as a modified risk tobacco product (MRTP),[8] in 2012, the FDA provided specific draft guidance for industry[9] regarding the types of scientific evidence to be expected in an MRTP application. The FDA outlined a step-by-step assessment program inspired by the pharmaceutical industry.

The basis for the science underlying an MRTP assessment is that smoking-related harm and disease are directly caused by the exposure to the toxicants found in smoke from combusted tobacco.[10] As stated by the US Institute of Medicine, cessation is the "gold standard" for the assessment of an MRTP, providing *"an aspirational goal for risk and exposure."*[11] Based on these principles, the assessment should demonstrate that switching to a candidate MRTP leads to a significant reduction in exposure to harmful chemicals, which in turn leads to a significant reduction in risk, and that both reductions approach those observed in smoking cessation.

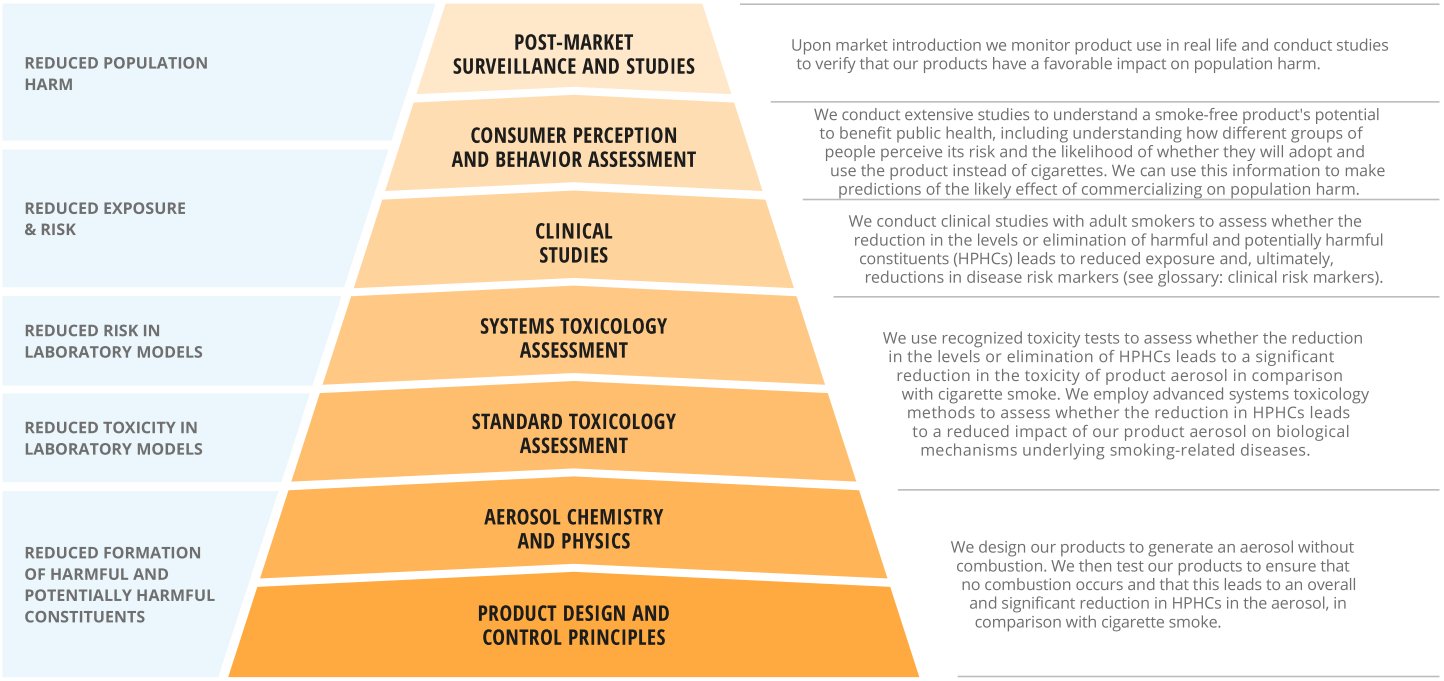
PMI'S MRTP APPLICATION

PMI established its multi-step assessment program (see Figure 2) applying internationally accepted scientific and quality standards along the principles set in the FDA guidance.[12**] Through our program, we assess the extent to which switching to EHTP results in a reduction of exposure to harmful or potentially harmful chemicals and the risk of smoking-related diseases by evaluating how different they are from continued smoking and how similar they are to smoking cessation.

PMI's MRTP application for EHTP provides a detailed mapping of that process, showing how PMI developed studies to address the statutory requirements and the FDA's draft guidance using internationally accepted toxicity tests, advanced systems toxicology methods, clinical studies as well as innovative perception and behavior studies. Importantly, PMI's MRTP application addresses both pillars of the harm reduction equation.

The following presents an overview of each step of our assessment program and the results generated for EHTP. Taken together, these steps provide the FDA with a comprehensive dossier in order to assess the impact of marketing EHTP in the US with claims of reduced risk of harm, reduced risk of tobacco-related diseases, or reduced exposure to harmful or potentially harmful chemicals when switching completely from cigarettes.

Figure 2. PMI's step-by-step assessment program is in line with FDA draft guidance for MRTPs and applied to EHTP.



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8 The term modified risk tobacco product (MRTP) is defined by the US Family Smoking Prevention and Tobacco Control Act, as "any tobacco product that is sold or distributed for use to reduce harm or risk of tobacco-related diseases associated with commercially marketed tobacco products." (Family Smoking Prevention and Tobacco Control Act, 2009).

9 FDA, Modified Risk Tobacco Product Applications: Draft Guidance for Industry, (2012).

10 Center for Disease Control and Prevention, How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of The Surgeon General (2010), p.9 (http://www.cdc.gov/tobacco/data_statistics/sgr/2010/index.htm?s_cid=cs_1843).

11 Institute of Medicine, Scientific Standards for Studies on Modified Risk Tobacco Products (2011), p.202 (https://www.nap.edu/catalog/13294/scientific-standards-for-studies-on-modified-risk-tobacco-products).

12 See reference 29 in EHTP-related publications.

**For supporting publications please see EHTP-related publications on page 10.

PRODUCT DESIGN AND CONTROL PRINCIPLES

PMI's processes and practices ensure that the product meets quality standards and specified performance parameters, including product design principles, manufacturing quality controls and a change management process. The processes and related data establish that EHTP heats tobacco at controlled temperatures below those needed for tobacco to burn and that there is no combustion.

REDUCING INDIVIDUAL RISK

Aerosol Chemistry and Physics

PMI conducted thorough scientific studies to assess the EHTP aerosol chemistry (formation of harmful and potentially harmful compounds or HPHCs), aerosol physics and indoor air chemistry. The data demonstrated that the aerosol generated by the EHTP had levels of HPHCs that on average were 90% to 95% lower than those measured in the smoke of a standard reference cigarette (3R4F). In addition, the EHTP aerosol did not negatively affect indoor air quality.

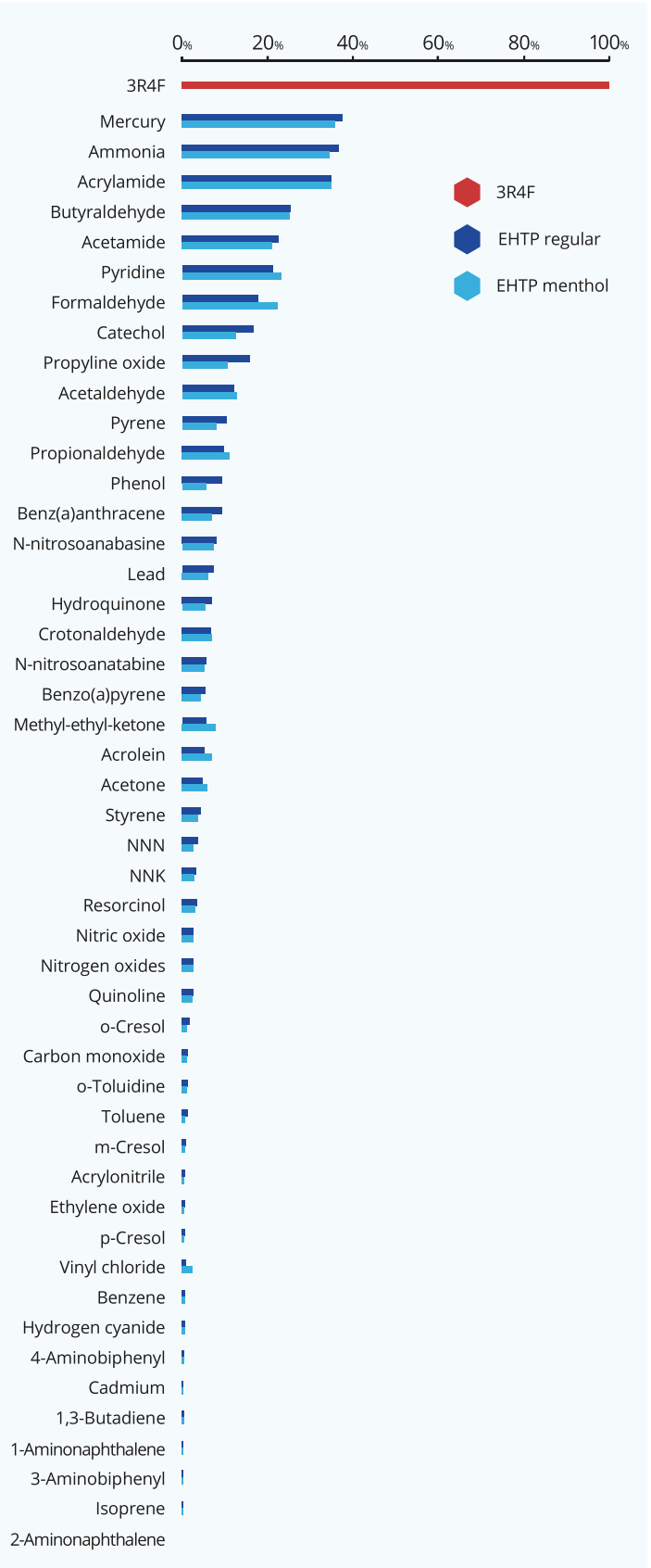
- Of the 54 HPHCs PMI measured (see Figure 3), the FDA requires tobacco manufacturers to quantify 18 for reporting. Of these, the levels were on average 90% lower than those measured in the smoke from a standard reference cigarette (3R4F).[13, 14] Similarly, the levels of 15 chemicals classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens were reduced on average by more than 95% compared to a reference cigarette.
- Indoor air chemistry studies were conducted to determine the concentrations of 18 different analytes under ISO-defined indoor environmental conditions (residential, office, hospitality). Only nicotine and acetaldehyde were detected above baseline levels, and their concentrations were well below threshold levels for exposure under a variety of US and international exposure standards.[15]

Standard Toxicological Assessment

In vitro and *in vivo* studies were conducted to determine whether EHTP aerosol was significantly less toxic in a laboratory setting than cigarette smoke. The data demonstrated that EHTP aerosol is significantly less toxic than the smoke from a standard reference cigarette (3R4F).

- Three *in vitro* assays were conducted to compare the toxicity of EHTP aerosol with cigarette smoke. In the first test (Neutral Red Uptake), the *in vitro* cytotoxicity of the EHTP aerosol was reduced by approximately 90% (see Figure 4). In the second test (Ames Assay), no bacterial mutagenicity was observed at the tested dose range for EHTP, whereas reproducible mutagenic responses were observed for cigarette smoke. In the third test (Mouse Lymphoma Assay), which investigates mammalian mutagenicity, the aerosol from EHTP was at least eight-fold less mutagenic.[13, 14]
- In two inhalation toxicity *in vivo* studies, exposure in the laboratory to EHTP aerosol resulted in reduced exposure to HPHCs, which led to reduced lung inflammation, which in turn led to reduced respiratory organ impairment findings.[16, 17, 18, 19]

Figure 3. PMI measured 54 harmful or potentially harmful compounds (HPHCs) in the EHTP aerosol compared to a standard reference cigarette (3R4F). The HPHCs flagged by the FDA and the International Agency for Research on Cancer (IARC) were reduced on average by 90%-95%.



Innovative Systems Toxicology Assessment

Systems toxicology relies on state-of-the-art high-throughput experimental technologies and advanced computational sciences to determine whether reduced toxicity leads to reduced risk in laboratory models. Systems toxicology enables a detailed assessment of the disease-relevant biological mechanisms affected by exposure to toxicants.[20, 21] Several studies were conducted to compare the effects of the EHTP aerosol with those of cigarette smoke. All studies demonstrate that exposure to EHTP aerosol significantly reduced biological effect when compared with exposure to cigarette smoke.

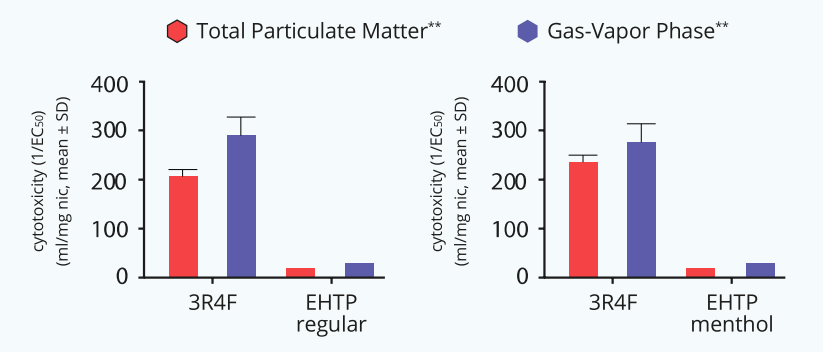
- Four studies conducted *in vitro* to compare the biological effects of the EHTP aerosol with those of cigarette smoke on human organotypic tissue cultures of oral,[22] gingival,[23] nasal,[24] and bronchial[25] epithelia. In all studies, the EHTP aerosol had a significantly reduced effect on all mechanisms affected by cigarette smoke.
- A study was conducted in a laboratory model that develops atherosclerotic plaque and emphysema when exposed to cigarette smoke.[26] In this study, exposure to either cigarette smoke or EHTP aerosol lasted for eight months. In addition, another group was first exposed for two months to cigarette smoke and then randomized to either EHTP aerosol (switching) or fresh air (cessation). Switching to EHTP aerosol was shown to reduce the development of both atherosclerosis and emphysema in a manner similar to smoking cessation. A detailed analysis of the molecular mechanisms affected by smoke exposure in the lung showed that switching to EHTP aerosol reduced the overall biological impact in a way that approached cessation and that long-term exposure to the EHTP aerosol has only little effect on these mechanisms compared with cigarette smoke exposure.[27, 28]

Clinical Studies

PMI's application to the FDA includes three types of clinical studies: pharmacokinetic/pharmacodynamics (PK/PD) studies; one-week reduced-exposure studies in confinement; and three-month reduced-exposure ambulatory studies. PMI is also conducting a 6+6-month exposure-response study. The clinical trials are conducted following Good Clinical Practices, reviewed by an institutional review board or an independent ethics committee, and registered on the US government's publicly available website www.clinicaltrials.gov, which is maintained by the National Institutes of Health. The eight completed studies demonstrated that EHTP:

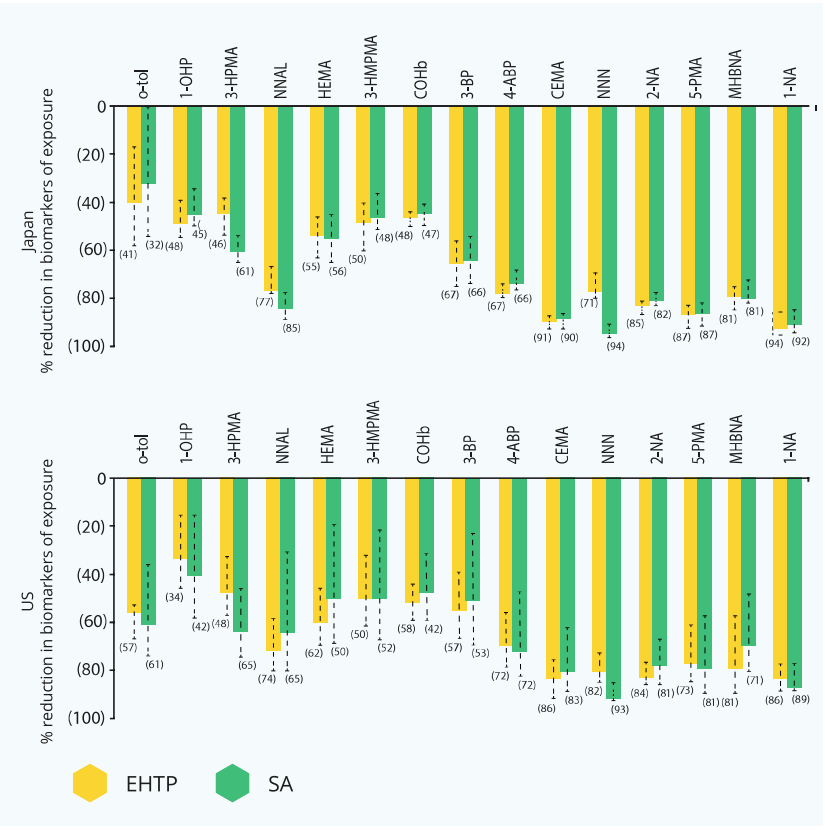
1. delivers nicotine at levels comparable to cigarettes, an important fact to ensure that adult smokers will find the product an acceptable substitute for cigarettes;
2. significantly reduces exposure to 15 harmful toxicants in adult smokers who switched to EHTP to a degree approaching that of cessation over the study period (see Figure 5);[29, 30, 31] and
3. led to favorable changes in clinically relevant risk markers linked to smoking-related diseases and known to reverse upon cessation over the study period.[32]

Figure 4. The reductions in HPHCs lead to reduced toxicity in the laboratory. For example, the Neutral Red Uptake assay, which measures cytotoxity, demonstrates significant reductions in cell death when comparing cigarette smoke and EHTP aerosol.



**Cigarette smoke and EHTP aerosol are composed of these two separate phases.

Figure 5. The reductions observed in the laboratory are reflected under conditions of actual use. Clinical studies conducted in Japan (top) and the US (bottom) demonstrate the percent reduction in biomarkers of exposure for smokers who switched to EHTP (gold bars) compared to smokers who abstained from smoking (green bars) after three months.



POPULATION BENEFIT

Consumer Perception and Behavior Studies
PMI conducted nine Perception and Behavior Assessment (PBA) studies in the US with over 10,000 participants to assess risk perception, comprehension, and intention to use the EHTP among various adult consumer groups: adult smokers, young adult never smokers, adult former smokers and adult never smokers. The studies can support an assessment in a premarket setting of EHTP's potential to impact population harm.

- A series of PBA studies assessed the likelihood of initiation among non-users of tobacco products. Overall, these studies demonstrated that it was largely only attractive to adult smokers.
- The same PBA studies also showed that users and non-users of tobacco products understood that the EHTP is not risk-free and is addictive.
- The same PBA studies also showed that the EHTP communications did not significantly affect the intention to quit among those adult smokers who expressed an initial intention to quit. Additionally, they understood that the best way to reduce the risk of tobacco-related diseases is to completely quit tobacco use.
- Overall, the studies also showed that material with effectiveness claims generated substantial intention to use EHTP among existing tobacco users, up to 39%.
- Further, one of the PBA studies which assessed actual use among adult smokers showed that after six weeks approximately 15% of the study participants had switched from cigarettes to either exclusive (≥95% tobacco use), or predominant (≥70% tobacco use), use of EHTP. The availability of EHTP did not lead to an overall increase in study participants' total tobacco product consumption.

Population Health Impact Modelling
PMI has developed, validated and tested a Population Health Impact Model (PHIM) using well-established methods in mathematical modelling and simulation analysis.[33] Using hypothetical assumptions on the likelihood of EHTP use, combined with estimated changes in relative disease risk, PMI has conducted multiple simulations to estimate the overall impact of EHTP on the health of the US population. In all but the most unlikely simulations, the introduction of EHTP resulted in lower tobacco-related mortality.[34]

Post-Market Research
PMI has developed and will conduct a post-market assessment program consisting of safety surveillance, cross-sectional surveys (one time observations of a population sample) and cohort studies (monitoring recruited participants over defined period) to allow for collection of safety data, prevalence of use over time, including initiation and cessation, use patterns, and to evaluate the biomarkers of exposure and effect. PMI will submit the findings from the Post-Market Assessment Program to FDA on an annual basis to ensure that the product continues to be of benefit to the overall health of the US population.

REAL-LIFE DATA FROM JAPAN

The data from Japan show that a significant proportion of adult EHTP users switch to the product exclusively (over 70% in December 2016) with the proportion of exclusive users increasing over time. Early cross-sectional studies on the adult population seem to indicate that the proportion of initiation and relapse associated with EHTP are in the low single digits. These real-life observations confirm the PBA study results conducted in the US.

Conclusion

The Tobacco Control Act established a mechanism that can ensure that products, which hold out the hope of presenting less risk of harm are actually tested, reviewed, and made available in the marketplace. The FDA has stated that the provisions of the Act covering MRTPs *"may be valuable tools in the effort to promote public health by reducing the morbidity and mortality associated with tobacco use, particularly if companies take advantage of these provisions by making bold, innovative product changes that substantially reduce, or even eliminate altogether, the toxicity or addictiveness of tobacco products, or both."*[35]

PMI developed an assessment program in line with the stepwise approach also espoused by the FDA. Applying this program to its EHTP, PMI has seen that the significant reductions in the harmful or potentially harmful compounds in the EHTP aerosol compared with cigarette smoke are reflected in significant reductions in each progressive step of the program. This is coupled by results demonstrating a lack of interest among unintended audiences and interest along with proper understating by the intended audience. These results gave us confidence to apply for EHTP through the MRTP pathway.

REFERENCES

13 See reference 26 in EHTP-related publications. **14** See reference 27 in EHTP-related publications. **15** See reference 20 in EHTP-related publications.
16 See reference 35 in EHTP-related publications. **17** See reference 28 in EHTP-related publications. **18** See reference 21 in EHTP-related publications.
19 See reference 12 in EHTP-related publications. **20** See reference 6 in EHTP-related publications. **21** See reference 30 in EHTP-related publications.
22 See reference 36 in EHTP-related publications. **23** See reference 37 in EHTP-related publications. **24** See reference 18 in EHTP-related publications.
25 See reference 7 in EHTP-related publications. **26** See reference 14 in EHTP-related publications. **27** See reference 22 in EHTP-related publications.
28 See reference 15 in EHTP-related publications. **29** See reference 3 in EHTP-related publications. **30** See reference 4 in EHTP-related publications.
31 See reference 16 in EHTP-related publications. **32** See reference 17 in EHTP-related publications. **33** See reference 34 in EHTP-related publications.
34 See reference 13 in EHTP-related publications.

35 FDA, Modified Risk Tobacco Product Applications: Draft Guidance for Industry, (2012).

LATEST EVENTS

GLOBAL FORUM ON NICOTINE

WARSAW, POLAND, 15-17 JUNE 2017

At the 2017 edition of the Global Forum on Nicotine, an international conference focused on the role of safer nicotine products that help people stop smoking, PMI scientists presented data from our perception and behavior program, as well as clinical and long-term studies.

Dr. Moira Gilchrist explained in plenary how PMI's scientific assessment approach is planned to minimize the unintended consequences – dual EHTP and cigarette use for example – of switching to EHTP.

Interested policymakers, healthcare professionals, academic researchers and others were able to learn about EHTP's actual use patterns, its perceived risks and intention to use, in addition to its ongoing post-market assessment. Furthermore, clinical data on biomarkers of exposure with Platform 2 and on nicotine pharmacokinetics and subjective effects in Platform 3 were available for discussion.

Find out more about PMI's presence at the event here: https://www.pmiscience.com/events/global-forum-nicotine-gfn-2017

21st WORLD CONGRESS OF EPIDEMIOLOGY

SAITAMA, JAPAN

19-22 AUGUST 2017

Organized by the International Epidemiological Association, the World Conference gathered over 1,000 professionals from about 60 countries to discuss the latest developments in the field and strengthen relationships around the world. PMI moderated a session on environmental epidemiology, in which it also delivered an oral presentation on its methods and findings on the prevalence and patterns of tobacco use in Japan after the commercialization of its EHTP.

Find out more about PMI's presence at the event here: https://www.pmiscience.com/events/21st-world-congress-epidemiology-wce2017

ICBBS 2017: 19th INTERNATIONAL CONFERENCE ON BIOINFORMATICS AND BIOMEDICAL SCIENCE

TOKYO, JAPAN

28-29 MAY 2017

The 19th International Conference on Bioinformatics and Biomedical Science brought together academic scientists and researchers to exchange research on all aspects of Bioinformatics and Biomedical Science, as well as providing a forum to present and discuss the most recent innovations, trends, and concerns. PMI co-chaired the opening session of the conference, introducing its work on systems biology and the sbvIMPROVER challenge.

Find out more about PMI's presence at the event here: https://www.pmiscience.com/events/icbbs-2017-19th-international-conference-bioinformatics-and-biomedical-science.

SHARING AND VERIFYING PMI'S RESEARCH - sbvIMPROVER DATATHONS 2017

Our systems toxicology program uses large datasets to predict the extent of damage to the body from exposure to toxic substances. sbvIMPROVER is a crowd-sourcing platform we built and use to validate that research. We do so through challenges that ask scientists to independently derive methodologies solving scientific questions of interest and datathons focusing on analyzing and interpreting data. We can then gauge the extent to which our own research and results are in line with these crowd-sourced results. Since its inception in 2011, more than 600 scientists from nearly 200 institutions across the globe have taken part in four challenges and two datathons. And the results from the challenges have validated PMI data.

These verifications are organized through a series of challenges. The closing symposium was held in Tel Aviv on May 4, 2017, where the challenge winner presented her method and results.

Find out more about the event here: https://www.pmiscience.com/events/sbv-improver-epigenomics-challenge-2017

GLOSSARY

AEROSOL

An aerosol is a suspension of fine solid particles and/or liquid droplets in a gas (usually air). Cigarettes generate a smoke aerosol that is the result of the combustion (burning) of tobacco, and contains carbon-based solid particles. While smoke is an aerosol, not all aerosols are smoke.

PMI's smoke-free products do not produce smoke because they do not burn tobacco. Instead, they generate a nicotine-containing aerosol, either by heating tobacco or through other technologies that do not involve combustion.

Consumers typically use the term vapor to refer to the aerosol generated from heated tobacco products or other nicotine-containing products.

BIOMARKERS

Biomarkers can be classified into biomarkers of exposure and clinical risk markers.

- Biomarkers of exposure: indicate exposure to a potentially hazardous substance. In our case, the biomarker may be a cigarette smoke constituent or metabolite that is measured in a biological fluid or tissue and that can provide a measure of internal dose (i.e., the amount of the constituent taken up into the body).
- Clinical risk markers: a measurable biochemical, physiological, behavioral, or other alteration within an organism that, depending upon the magnitude, can be recognized as associated with an established or possible health impairment or disease.

CLINICAL RISK MARKERS

See Biomarkers

COMBUSTION

Combustion is the process of burning a substance in oxygen. When a cigarette is lit, the combination of tobacco (fuel) and oxygen in the air generates a self-sustaining combustion process that consumes the tobacco. The combustion of tobacco results in the formation of smoke (which contains a range of chemical constituents), heat and ash. The high heat associated with combustion leads to the thermal breakdown of the tobacco when it is burned, resulting in the production of many of the toxicants found in cigarette smoke.

MODIFIED RISK TOBACCO PRODUCT (MRTP)

The term used to classify a potentially less harmful products by the US Family Smoking Prevention and Tobacco Control Act (2009), which granted to the FDA authority to regulate tobacco products and to authorize claims of reduced risk. MRTP is defined as *"any tobacco product that is sold or distributed for use to reduce harm or risk of tobacco-related diseases associated with commercially marketed tobacco products."*

PHARMACOKINETIC STUDIES

Measure how a substance, such as nicotine, is absorbed by the body. This helps in determining the extent to which adult smokers would find the alternative product an acceptable substitute for cigarettes, although other factors such as taste and product design are important elements in determining consumer acceptability. In addition to the kinetic profile of nicotine, we also monitor the safety of the users of the product under investigation (e.g., data on vital signs, clinical biochemistry, and adverse events).

REDUCED RISK PRODUCT (RRP)

Reduced-Risk Product (RRP) is the term PMI uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes. PMI's RRPs are in various stages of development and commercialization, and PMI is conducting extensive and rigorous scientific studies to determine whether we can support claims for such products of reduced exposure to harmful and potentially harmful constituents (HPHCs) in smoke and, ultimately, claims of reduced disease risk, when compared with smoking cigarettes. Before making any such claims, we will rigorously evaluate the full set of data from the relevant scientific studies to determine whether they substantiate reduced exposure or risk. Any such claims may also be subject to government review and authorization, as is the case in the US today.

REFERENCE CIGARETTE (3R4F)

A standard cigarette for laboratory testing provided by the University of Kentucky. The current version is known as 3R4F and is used for non-clinical investigations by tobacco manufacturers, contract and government laboratories, and academic institutions.

STANDARD TOXICOLOGY

To compare whether the reduction in the levels of harmful and potentially harmful chemicals generated by our smoke-free products reduces the toxicity of their aerosol, we perform a range of standard toxicological assays. For example, we have conducted a number of widely used *in vitro* assays comparing the toxicity of our smoke-free products' aerosol to cigarette smoke. These include, but are not limited to:

- The Neutral Red Uptake cytotoxicity assay (measuring mammalian cell toxicity)
- The Ames bacterial mutagenicity assay (measuring bacteria cell mutations)
- The Mouse Lymphoma mammalian mutagenicity assay (measuring mutations in mammalian cells)

We have also conducted *in vivo* assays of different durations, including acute and repeated dose inhalation studies in accordance with Organization for Economic Co-operation and Development (OECD) Test Guidelines.

SYSTEMS TOXICOLOGY

Systems toxicology (pub. 6 and 30) integrates standard toxicology with advanced experimental and computational methods (including large-scale molecular measurements, imaging technologies, mathematical modeling and computational biology) to identify the biological mechanisms triggered by exposure to toxic substances and quantify their biological impact.

EHTP-RELATED PUBLICATIONS

1. Brossard P, Weitkunat R, Poux V, Lama N, Haziza C, Picavet P, Baker G and Lüdicke F (2017) Nicotine pharmacokinetic profiles of the Tobacco Heating System 2.2, cigarettes and nicotine gum in Japanese smokers. **Regulatory Toxicology and Pharmacology**, 89:193-199. (PMID: 28760390).

2. Gonzalez Suarez I, Martin F, Marescotti D, Guedj E, Acali S, Johne S, Dulize R, Baumer K, Peric D, Goedertier D, Frentzel S, Ivanov N, Mathis C, Hoeng J and Peitsch MC (2016) *In vitro* Systems Toxicology assessment of a candidate Modified Risk Tobacco Product shows reduced toxicity compared to a conventional cigarette. **Chemical Research in Toxicology**, 29:3-18. (PMID: 26651182).

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5. Haziza C, De La Bourdonnaye G, Skiada D, Ancerewicz J, Baker G, Picavet P and Luedicke F (2017) Biomarker of exposure level data set in smokers switching from conventional cigarettes to Tobacco Heating System 2.2, continuing smoking or abstaining from smoking for 5 days. **Data in Brief**, 10:283-293. eCollection 2017. (PMID: 27995164).

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9. Iskandar AR, Titz B, Sewer A, Leroy P, Schneider T, Zanetti F, Mathis C, Elamin A, Frentzel S, Schlage W, Martin F, Peitsch MC, and Hoeng J (2017) Systems Toxicology Meta-Analysis of *In Vitro* Assessment Studies: Biological Impact of a Modified-Risk Tobacco Product Aerosol Compared with Cigarette Smoke on Human Organotypic Cultures of the Respiratory Tract. **Toxicology Research**, 6:631-653. doi: http://dx.doi.org/10.1039/C7TX00047B.

10. Iskandar A, Martinez Y; Martin F, Schlage WK, Leroy P, Sewer A, Ortega-Torres L, Majeed S, Trivedi K, Guedj E, Frentzel S, Mathis C, Ivanov N, Peitsch MC, Hoeng J (2017) Comparative Effects of a Candidate Modified-Risk Tobacco Product Aerosol and Cigarette Smoke on Human Organotypic Small Airway Cultures: A Systems Toxicology Approach. **Toxicology Research (Cambridge)**, in press. doi: http://dx.doi.org/10.1039/C7TX00152E.

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PHILIP MORRIS INTERNATIONAL

YOU CAN CONTACT US HERE

FOR PRESS INQUIRIES

MEDIA@PMI.COM

+41 (0)58 242 4500

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