For many decades, the primary strategies for reducing the harm associated with cigarette smoking have been focused on preventing smoking initiation and promoting smoking cessation. Although smoking prevalence has declined in many countries over the last forty years, in the last ten years those declines have flattened in many OECD and other advanced countries such as Singapore. Globally, hundreds of millions of adults continue to smoke cigarettes. Based on World Health Organization estimates, over 1.1 billion people currently smoke cigarettes and, as a result of global population growth, this number is projected to remain largely unchanged over the next decade. For those 1.1 billion smokers, cigarettes can cause a number of serious diseases including cardiovascular disease, lung cancer and chronic obstructive pulmonary disease. In addition, smoking is addictive and it can be very difficult to stop.

For over a century, the basic design and use of cigarettes has not changed: shredded tobacco leaves are burned, which produces smoke. The cigarette smoker inhales this smoke which contains nicotine and a number of toxic substances. Many public health bodies agree that whilst nicotine is addictive, it is not the primary cause of smoking-related diseases. It is the other toxic substances that are generated by burning tobacco that are the principal problem in terms of health and mortality.

Through technological innovation and rigorous scientific assessment, Phillip Morris International (PMI) is developing a number of non-combustible nicotine and tobacco products that have the potential to significantly reduce individual risk and population harm when compared to smoking cigarettes. We refer to these products as ‘Reduced-Risk Products’, or ‘RRPs’, and PMI’s goal is to lead, at a global scale, an unprecedented effort to ensure that they ultimately replace cigarettes.

Tobacco Harm Reduction

The best way to avoid the harms of smoking is never to start, or to quit. For adult smokers who would otherwise continue to smoke cigarettes, providing them with low risk alternatives to cigarettes is the basis of ‘Tobacco Harm Reduction’. Recognizing that over a billion people are likely to continue to smoke cigarettes, the policy of Tobacco Harm Reduction is being put forward by a multitude of global stakeholders – including public health organizations, healthcare professionals and regulators – to complement the other major strategies of reducing smoking related harm (i.e., prevention and cessation).

For example, in May 2014, 53 prominent public health experts and leading scientists from over 18 countries wrote an open letter to the World Health Organization (WHO) urging the organization to support tobacco harm reduction. They wrote:

“There are now rapid developments in nicotine-based products that can effectively substitute for cigarettes with very low risks. These include, for example, e-cigarettes and other vapor products, low-nitrosamine smokeless tobacco such as snus, and other low-risk non-combustible nicotine or tobacco products that may become viable alternatives to smoking in the future.”

The letter concluded:

“The potential for tobacco harm reduction products to reduce the burden of smoking related disease is very large, and these products could be among the most significant innovations of the 21st century – perhaps saving hundreds of millions of lives.”

Tobacco policy advocates acknowledge that Tobacco Harm Reduction depends on smoker acceptance of alternative products. This is part of the widely-accepted ‘harm-reduction equation’, where harm reduction is the outcome of a product’s risk reduction effect multiplied by the number of smokers who switch to the product (which is itself determined by the product’s appeal).
PMI believes that effective Tobacco Harm Reduction is best achieved by offering current adult smokers who want to continue to use nicotine products a range of novel products that are substantially less toxic than cigarettes. However, the potential individual and public health benefit of this approach will only be achieved if these novel products are scientifically substantiated to reduce risk and are also acceptable alternatives for current adult smokers who would otherwise continue to smoke cigarettes. At the same time, as these products are not risk-free, it is important that non-smokers (especially youth), former smokers and smokers who are motivated to quit do not initiate tobacco / nicotine use with these new products.

“...it is important to appreciate that a virtually harmless [product used] by only 1% of the population will have a lesser impact on the reduction of tobacco-related diseases than a somewhat more harmful [product used] by 80% of the total smoking population.”

Dr. Ernst Wynder

Development And Assessment

PMI is taking a thorough, systematic and stepwise approach to RRP assessment, based in large part on the U.S. Food and Drug Administration (FDA) draft guidance on the regulatory procedure for authorizing to market an RRP (referred to in U.S. law as a ‘Modified Risk Tobacco Product’, or ‘MRTP’). The draft guidance requires applicants to demonstrate that the RRP, as actually used, will (i) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, and (ii) benefit the health of the population as a whole, taking into account both the users of tobacco products and people who do not currently use tobacco products.

The objective of PMI’s assessment program is to demonstrate that RRPs have a risk reduction profile approaching that of smoking cessation. In the diagram shown below, the red line represents a cigarette smoker’s increased risk of disease over time, and the green line that smoker’s decreasing risk of disease following smoking cessation (these increases and decreases of risk are well documented by epidemiological studies). The yellow lines in the diagram show the aspiration PMI has for its RRPs – that is, to achieve changes in disease risk that approach those seen following smoking cessation, regarded by the U.S. Institute of Medicine as the gold standard for RRP assessment.

The assessment program integrates seven steps, designed to provide five levels of evidence once the program is completed:

1. Product Design and Control Principles
   Following the principles outlined above, RRPs are designed with two main criteria in mind: (1), the RRP should reduce the formation of harmful and potentially constituents (HPHCs) found in cigarette smoke and (2), the RRP should preserve as much as possible the sensory experience, nicotine delivery profile and ritual characteristics of cigarettes so that smokers find it easy to switch. This first step of the RRP assessment is designed to ensure that the product meets these criteria and that it is manufactured to appropriate quality standards.

2. Aerosol Chemistry and Physics
   In the second step we analyze the chemical composition of the aerosol generated by the RRP and quantify the reduction in formation of HPHCs in comparison with cigarettes. These reductions must be consistent across different potential usage patterns and environmental conditions. The analysis also evaluates whether any new HPHCs are generated by the RRP. The effects of the RRP on indoor air quality in comparison to cigarettes (benchmarked against national and international standards for exposure to environmental toxicants) are also determined.

3. Standard Toxicology Assessment
   The third step determines whether the reduced formation of HPHCs leads to reduced toxicity in laboratory models.
Toxicological studies are conducted both in vitro and in vivo. First, three commonly used in vitro assays (Neutral Red, Ames and Mouse Lymphoma) assess the cytotoxicity and genotoxicity of RRP aerosols in comparison with cigarette smoke. Second, the inhalation toxicity of RRP aerosols is analyzed in vivo according to the guidelines from the Organization for Economic Co-operation and Development (OECD).

4. Systems Toxicology Assessment

Our systems toxicology approach allows us to determine whether reduced toxicity in laboratory models leads to reduced risk in those models. First, we identify the biological mechanisms that are altered by cigarette smoke, capturing this knowledge in biological network models. These models are then used to analyze our product assessment datasets, allowing us to compare the network alterations caused by RRP aerosols with those caused by cigarette smoke. This process facilitates an early assessment of the reduced risk potential of RRPs.

21st Century Toxicology

Our systems toxicology approach is aligned with the goals and principles of ‘21st Century Toxicology’, as set-out in the US National Research Council’s landmark vision and strategy report. Also, the U.S. FDA has highlighted ‘modernizing toxicology’ as one of its priority areas and explicitly expressed an interest in new toxicology testing procedures that would improve the ability of models and measurements to predict product safety issues.

One component of our work in systems toxicology is the sbvIMPROVER platform. Based on the principles of crowdsourcing, the platform is used to independently verify the performance of methods and tools in computational biology, so as to facilitate the analysis of complex datasets and the interpretation of complex assessment studies. This work not only helps PMI in the assessment of RRPs, but should also be relevant to other industries that would benefit from the independent assessment of methods and study results.

For further information see www.sbvimprover.com.

5. Clinical Trials

The fifth step of the assessment program utilizes clinical studies to assess whether RRPs lead to reduced exposure and risk in adult smokers when compared to cigarette smoking. These studies are Ethics Committee approved and conducted according to the ICH guidelines for Good Clinical Practice. Typically, adult cigarette smokers are randomized into three groups – i) continued smoking, ii) cessation, or iii) switch to RRP – in studies ranging from one week to one year. Shorter studies are conducted in clinical confinement while longer studies are conducted in an ambulatory setting to assess whether the use of RRPs in near to real-world settings leads to a reduction in exposure to toxicants as well as to favorable changes in smoking-related clinical risk endpoints.

6. Consumer Perception and Behavior Assessment

The sixth step involves the measurement, prior to market introduction, of the likely effect of introducing an RRP on tobacco use behavior within populations. This step assesses the likelihood that adult smokers will switch from cigarettes to the RRP, and that non-smokers will not use the RRP. Integral to this process is the assessment of consumer understanding and perceptions of risk that any product communication (e.g., marketing communication) would generate.

7. Post-Market Studies and Surveillance

Once an RRP is on the market, it is necessary to conduct post-market surveys to understand how the product is used and by whom. Passive surveillance measures are used to gather spontaneous reports of adverse events related to RRP use. Furthermore, cohort studies (e.g. 5-year) complement this approach to determine the effect of switching to the product on exposure and clinical risk markers over longer time periods. Finally, population health impact modeling, which combines epidemiology-derived risk data, product use patterns and prevalence of the product, is used to estimate the impact of commercial introduction of an RRP on population harm.

iQOS

PMI’s first commercially available RRP is sold under the brand name iQOS. Instead of burning tobacco and creating smoke, iQOS heats tobacco just enough to release a vapor that provides consumers with nicotine and tobacco flavors but with a greater than 90% reduction of the HPHCs found in cigarette smoke.

A substantial amount of scientific evidence related to iQOS has already been compiled. The results are very encouraging and show that the reduction in exposure to HPHCs in adult smokers who switch to iQOS approaches that observed in people who quit smoking during the studies. Assessment of risk reduction in smokers who switch to iQOS is ongoing.
Conclusion
Reducing harm by offering current adult smokers the option of switching to RRPs is a viable policy that we believe should be pursued in addition to preventing initiation and promoting smoking cessation. However, its success will require rigorous science-based oversight to ensure that consumers and public health are both protected and can ultimately benefit from the introduction of RRPs. A number of countries have adopted laws that recognize these new categories of products. For example, the European Union’s 2014 Tobacco Products Directive establishes specific requirements for "novel tobacco products," including non-combustible tobacco products, and for electronic cigarettes. The U.S. Tobacco Control Act similarly establishes rules for bringing new tobacco products to market, and a detailed process for authorizing the sale of ‘MRTPs’. Both systems require a substantial body of evidence to be provided to regulators before novel products are introduced and PMI intends to submit an MRTP Application to the U.S. FDA towards the end of 2016. Our aim at PMI is to ensure that the science we conduct is comprehensive and of the highest possible standard, and we welcome scrutiny and review by external, independent scientists and relevant public bodies.

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