Pharmacists: An Opportunity to Reduce Smoking Rates Through Technology

Worldwide, 7 million people die each year from diseases related to smoking[1], with 78,000 lives per year being claimed in England alone[2]. It is the single greatest preventable cause of death and disability in the world.

With over 1 billion smokers globally, the World Health Organization predicts that even by the year 2025, this figure will still remain roughly the same[3].

To help accelerate the decline in smoking in the UK, public health bodies have adopted a harm reduction approach, recognising that nicotine, while addictive and not risk-free, is not the primary cause of smoking related diseases[4, 5, 6], but rather the toxic chemicals emitted in smoke from the combustion of tobacco in cigarettes that are to blame. They have also welcomed the introduction of nicotine-based smoke-free products, such as e-cigarettes, in order to encourage adult smokers to abandon smoking. However, e-cigarette uptake has plateaued over recent years[7], and a major reason for this is that many smokers report missing the ritual of hand-to-mouth gestures, as well as the taste and smell of real tobacco.

Within UK pharmacies, the current availability of nicotine replacement therapies (NRTs), smoking cessation drugs (such as bupropion and varenicline), tools and counselling services have been unable to meet the needs of the majority of smokers. Indeed, government research shows that the number of smokers attempting to quit cigarettes within primary care has been steadily declining in recent years[8].

Research published in the New England Journal of Medicine also shows that only 18 per cent of smokers who had switched to e-cigarettes and less than 10 per cent of those on NRTs were still smoke-free after 12 months[9]. This illustrates how significant a problem relapse is for smokers when searching for suitable and acceptable smoke-free alternatives.

The limited success of NRTs and e-cigarettes shows that there is an urgent public health requirement to introduce a greater range of nicotine-based smoke-free products that can satisfy smokers' needs and meet public health objectives in encouraging smokers to give up cigarettes permanently.

In meeting this global public health challenge, some tobacco companies have turned to science and technology to create novel smoke-free products that can better replicate the taste and ritual of tobacco consumption, whilst reducing the harm. These smoke-free alternatives aim to provide adult smokers with more realistic options that enable them to abandon cigarettes completely and move to less harmful alternatives.

Philip Morris International (PMI), has used science and technology to develop a novel, smoke-free, heated tobacco product (HTP) that is a less harmful alternative to continued smoking and yet remains acceptable to adult smokers who would otherwise continue to smoke. Unlike cigarettes, these HTPs heat but do not burn tobacco. The tobacco is heated to temperatures well below combustion (burning), in order to generate a nicotine-containing aerosol, without any smoke. Consequently, substantially lower levels of harmful chemicals are emitted than cigarettes.

Why do cigarettes cause disease?

When a cigarette is lit, oxygen and heat, combined with tobacco, initiates a combustion process, starting at 400°C, which consumes the tobacco. Temperatures reach 600-800°C within the combustion zone and when the cigarette is puffed, temperatures can exceed 900°C[10]. At such high temperatures, the combustion of tobacco results in the formation of heat, smoke and ash[11, 12].

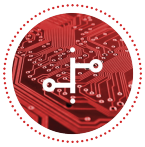
Cigarette smoke, produced by tobacco combustion, is a complex mixture of gas, liquid droplets and carbon-based solid particles. It also contains a mixture of more than 6000 chemicals, with approximately 100 of these identified by public health authorities (such as the US Food and Drug Administration) as harmful, or potentially harmful, to human health[13]. These harmful or potentially harmful chemicals (HPHCs) are likely responsible for the majority of smoking-related illnesses, such as cardiovascular disease, chronic obstructive pulmonary disease (COPD) and various forms of cancer.

Inhaled HPHCs initiate disease progression at the molecular level, including processes such as DNA alterations, release of inflammatory markers and generation of reactive oxygen species, which are followed by cellular and tissue level changes. Physiologic changes to organ structure and function, next occur, before finally presenting as clinical disease. Decades of epidemiological studies clearly show disease morbidity and mortality across populations are directly attributable to cigarette smoking.

PMI investigates these changes, undertaking research on toxic emissions and assessing the impact of HPHCs on biological processes at the molecular, cellular and physiological levels, as well as its effects on whole body systems and the wider population, via epidemiological studies.

For the development of new, harm-reducing smoke-free products, PMI studies the potential effects of any emissions using a complete systems biology approach, ultimately culminating in assessment of its products via human clinical and post-market surveillance studies, including population-wide epidemiological research.

Assessment steps for PMI's smoke-free product



Platform development

Toxicological assessment

Clinical assessment

Perception and behaviour

Long-term assessment

Smoking initiates molecular changes in cells, before bringing about the development of clinical disease, such as heart disease, COPD and cancer.

Content developed in partnership with Philip Morris Limited

The development of a heated tobacco product – a smoke-free alternative

Applying scientific research and technological innovation, PMI has developed a portfolio of smoke-free products that involve no combustion and generate no smoke or ash. These products contain nicotine, which is addictive and not risk-free, but have significantly reduced emissions of HPHCs.

PMI undertakes five major steps of assessment for its smoke-free products.

i) Platform development – involves initial product design and strict manufacturing controls, including physical and chemical analyses of all components of the aerosol to ensure product consistency;

ii) Toxicological assessment – studies to confirm whether the reduced formation of HPHCs leads to reduced toxicity and reduced risk of smoking-related diseases using in vitro and in vivo laboratory models;

iii) Clinical assessment – human clinical studies 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;

iv) Perception and behaviour – studies to assess whether non-smokers may be unintentionally drawn to using smoke-free products and smokers intending to quit are not dissuaded by them;

v) Long term assessment – post-market studies are undertaken to analyse data from real-world use, as well as epidemiological studies being carried out, to confirm if these smoke-free products reduce the risk of smoking-related diseases such as COPD, cardiovascular disease and lung cancer.

For any smoke-free alternative to be classed as a reduced-risk product, compared with continued smoking, it must fulfil two criteria:

1) It must be scientifically substantiated as significantly less harmful than cigarettes, and

2) It should be satisfying enough for current adult smokers so that they completely switch.

PMI has developed a smoke-free tobacco product that is based on these two criteria. For adult smokers, it offers an acceptable and scientifically substantiated smoke-free alternative, whilst reducing harm.

Philip Morris International's tobacco heating system (THS), called IQOS. PMI's THS consists of three components: (i) tobacco stick – a novel patent-pending processed tobacco product, (ii) a holder, containing an electronic heating blade, onto which the tobacco stick is inserted, and (iii) a charger – used to recharge the holder after each use.

PMI's Tobacco Heating System (THS): A novel smoke-free alternative

The new category of smoke-free product, developed by PMI, uses real tobacco.

Commercially called IQOS, it utilises a novel heat control technology which heats, but does not burn tobacco.

As a novel class of HTP, IQOS was developed with the aim of providing adult smokers, who would otherwise continue to smoke, with an acceptable smoke-free alternative that is better able to emulate the taste and ritual characteristics of tobacco consumption, whilst significantly reducing the harm.

Tobacco is heated to temperatures well below combustion (burning), generating a nicotine-containing aerosol. Since no combustion is involved and no smoke is generated, IQOS emits on average 95 per cent lower levels of HPHCs compared to cigarettes*. Chemical analyses confirm that IQOS generates a liquid-based inhalable aerosol consisting of liquid droplets and gas, and an absence of carbon-based solid particles.

The Science behind THS

Unlike cigarettes, IQOS uses proprietary heat control technology and an internal blade that heats a specially designed tobacco stick to a maximum temperature of 350°C – well below the 400°C required for combustion.

Although the heating blade reaches 350°C, most of the tobacco remains below 250°C[14]. At this temperature nicotine is aerosolised. Because no combustion occurs, the inhaled aerosol is fundamentally different in its composition compared to cigarette smoke, with significantly reduced formation of HPHCs.

As evidenced by both PMI's and several independent studies, chemical analyses confirms that on average IQOS emits 95% lower levels of HPHCs than smoke from a standard reference cigarette* (known as, 3R4F). Publications relating to these analyses can be found at: *www.pmiscience.com/library*.

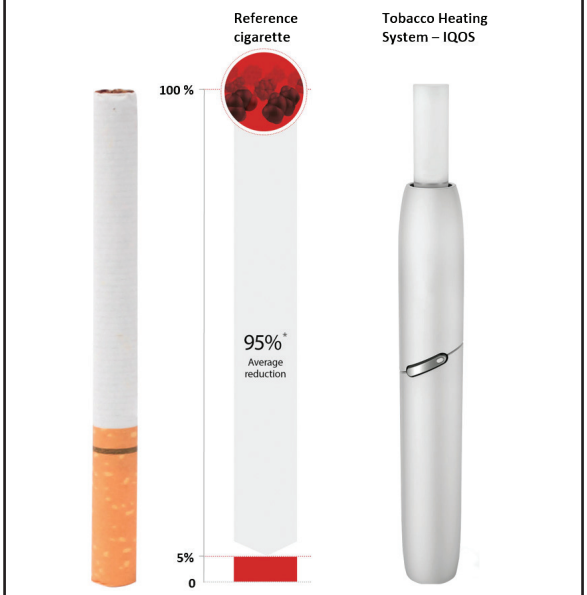
To evaluate any potential biological impact as a consequence of the aerosol emitted by IQOS, PMI has applied its scientific assessment program, including studies (in vitro and in vivo) at the molecular, cellular and physiological level, as well as human clinical trials, with the objective of creating a product that:

i) Potentially reduces risk of harm from tobacco-related diseases for those adult smokers who would otherwise continue to smoke, and

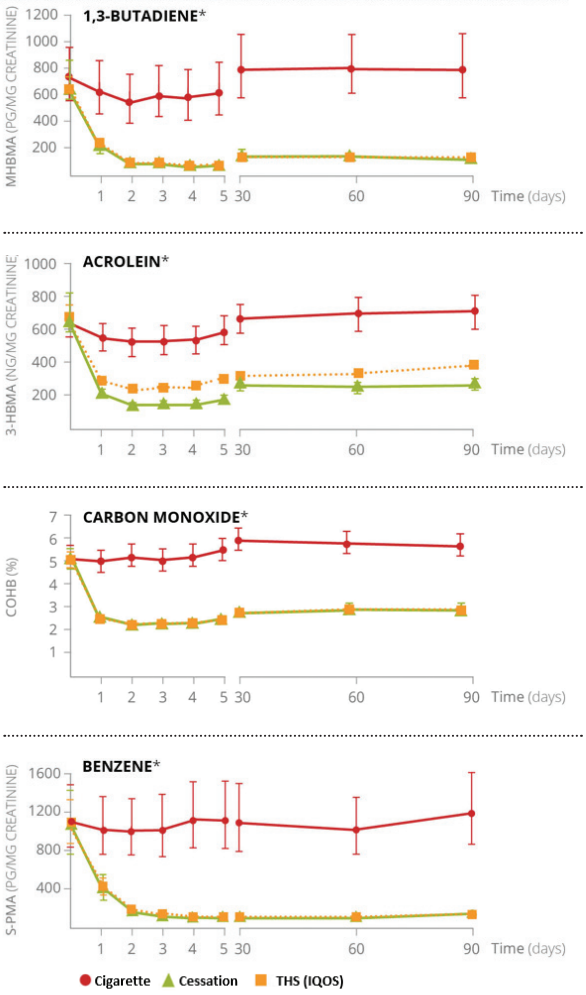
ii) Contributes to public health of the wider population by switching as many individual adult smokers, who would otherwise continue smoking, to a less harmful smoke-free alternative, as well as eliminating the production, and therefore, exposure of smoke to non-smokers.

Does completely switching to THS reduce the negative health effects of continued smoking?

Quitting smoking is the best way for smokers to reduce the harm from smoking. Therefore, the biological profile of smokers, following smoking cessation, serves as the aspirational goal for the development of a less harmful, smoke-free alternative, for those adult smokers who would otherwise continue smoking cigarettes.



*IQOS emits on average 95% lower levels of HPHCs compared to cigarettes**



Selected 4 HPHCs, and corresponding biomarkers: switching completely to IQOS brings a reduction in their blood/urinary levels similar to that of smoking cessation

Diseases caused by smoke from cigarettes are multifaceted and complex, with multiple physiological pathways affected, and clinical disease developing over many years of consumption or exposure.

Exposure to smoke-emitted HPHCs causes the dysregulation of molecular and cellular pathways, which affect multiple organ systems, bringing about a range of physiologic effects within the human body. Some these interfere with a range of mechanistic processes, causing inflammation, oxidative stress, platelet activation and faulty lipid metabolism.

To examine the effects of IQOS aerosol, as well as any potential genetic and cellular toxicity, a range of in vitro studies, including use of modelled airway cells[15], demonstrated a substantial reduction in the toxicity of IQOS aerosol as compared to cigarette smoke. This research, as well as other supporting data, has been peer-reviewed and published and can be found at: *www.pmiscience.com/library* and also on Science INTERVALS platform: *www.intervals.science.*

To investigate whether completely switching to IQOS reduces the harm caused by smoking, PMI has conducted further preclinical in vivo studies, using animal models[16, 17, 18], to examine the effects of IQOS aerosol exposure, in relation to any potential development for cardiovascular disease, COPD or lung cancer development as well as conducting human clinical trials, which compare the effects of switching adult smokers to IQOS versus that of continued smoking. These studies examine the physiological impact of IQOS on the body, as well as any potential impact on biological networks and involved in the development of smoking related diseases, such as cardiovascular disease, COPD and lung cancer. A snapshot of some of the results from PMI's human clinical studies is outlined within this article and detailed information can also be found on the PMI Science website: *www.pmiscience.com/library.*

Human Clinical Studies

Reduced Exposure to Harmful Chemicals

In assessing the human body's IQOS aerosol exposure, 5-day and 90-day clinical reduced exposure studies were carried out in Poland and Japan[19, 20, 21]. These studies measured reliable and validated biomarkers in the blood and urine that represented exposure to selected HPHCs. These HPHCs were chosen because they had been identified by the World Health Organization (WHO) and US Food and Drug Administration (FDA) as of particular concern and necessary for reduction in cigarette smoke[22, 23]. The results revealed that levels of 15 biomarkers of exposure in participants switching completely to IQOS were comparable to the levels of those who quit smoking for the duration of the study. In both cases, the levels remained significantly below those observed in subjects who continued smoking during the study.

The effects of switching to IQOS or smoking abstinence on biomarkers of exposure levels for 4 selected HPHCs are shown. These have been selected as they have been identified by regulatory bodies as being of particular interest due to their presence in cigarettes smoke, known toxicity and implicated involvement in carcinogenesis, cardiovascular disease and respiratory illnesses. A total of 15 biomarkers were investigated, all of which displayed the same trend as the 4 selected HPHCs shown. A similar clinical study conducted in the U.S. (NCT01989156) showed comparable results.

6 month Exposure Response Study – assessing biological and functional changes in smokers switched to IQOS

To assess whether, reduced exposure to HPHCs may have a potential positive impact on smokers' biological profile, a clinical study, called the Exposure Response Study[24], was carried out in the U.S. (NCT 02396381). This involved 984 adult smokers who consumed on average 19 cigarettes per day for a period of about 26 years. To assess whether there was an improvement in their biological and functional profile, the study compared one half of this group of adult smokers, randomised to continue smoking combustible cigarettes, against the other half that had been switched to IQOS. A selection of 8 clinical risk endpoints (CREs, i.e., measures of biological response, or biomarkers) were selected as they are known to be negatively affected by smoking and are expected to improve upon cessation. These CREs reflect various mechanistic pathways (lipid metabolism, endothelial

function, inflammation, oxygen delivery, oxidative stress, lung function, platelet function, and carcinogenesis) that are associated with smoking-related diseases, such as cardiovascular disease, respiratory disease, and lung cancer. After switching from smoking to IQOS for 6 months, all 8 biomarkers showed favourable changes in the same direction as that with smoking cessation, and statistically significant improvements were observed in 5 out of 8 co-primary CREs. Smokers who predominantly used IQOS showed improved biological effects relative to those who continued smoking, with similar nicotine levels in both groups.

In conclusion, switching from combustible cigarettes to heated tobacco brought about favourable biomarker outcome profiles related to cardiovascular health, COPD, and cancer.

Data from a 6-month extension study (NCT 02649556), to accompany the Exposure Response Study, is currently undergoing independent peer review and will be communicated when this is published.

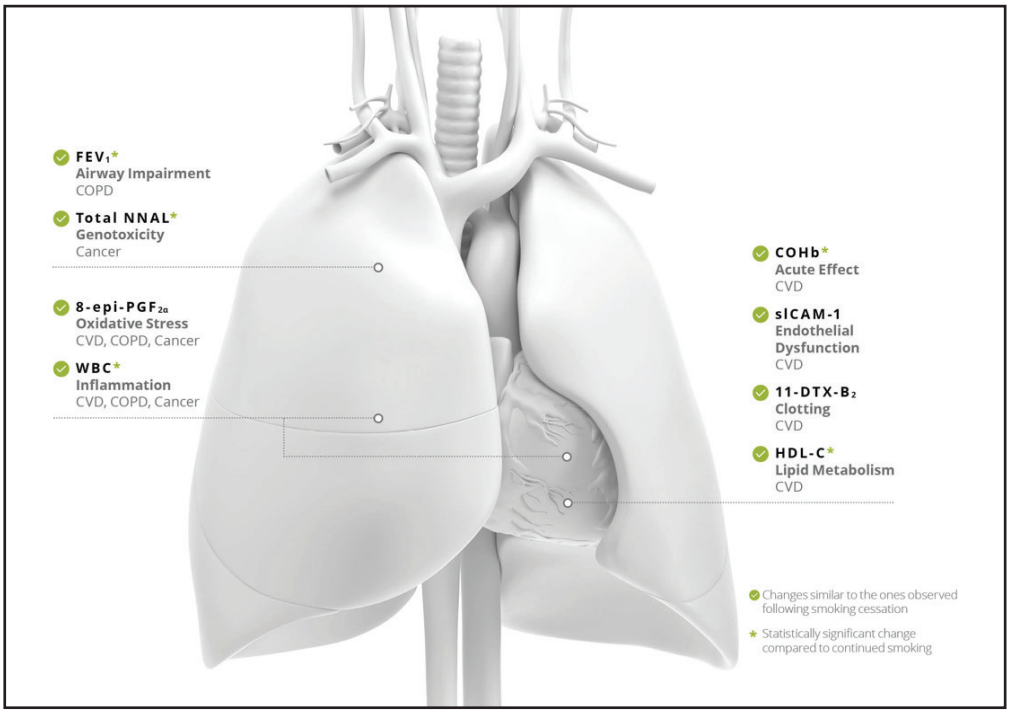
Perception, behaviour and long term assessments of THS

Long-term perception and behaviour studies have also been carried out to assess the effect of information provided on IQOS. These consistently show that the manner by which potential risks and benefits of IQOS are communicated to consumers, have generated substantial interest amongst adult smokers with no intention to quit smoking. At the same time, for smokers who expressed an intention to quit smoking, the communication materials did not significantly alter their intention to quit nicotine and tobacco use altogether[25].

These findings support the potential of IQOS in contributing to tobacco harm reduction at a population level.

Pharmacists and the future of smoke-free products

Given the ongoing challenge that smoking presents to public health in the UK and the reluctance of many smokers to embrace cessation or vaping products, pharmacists can play an important role in informing smokers of emerging alternatives, such as heated tobacco, which could help the UK stamp out smoking forever.



Simple schema of lungs and heart. All CREs (green ticks) shifted in the same positive direction as for smoking cessation, with 5 out of 8 of these being statistically significant (green asterisks)

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