In the District Court
Held at Wellington

CRI-2017-085-001107

between: **Ministry of Health**
Prosecutor

and: **Philip Morris (New Zealand) Limited**
Defendant

Brief of evidence of Moira Gilchrist

Dated: 09TH February 2018

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Before: TBC

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BRIEF OF EVIDENCE OF MOIRA GILCHRIST

Introduction

1 I am the Vice President, Scientific & Public Communications at Philip Morris International ("PMI"). Philip Morris (New Zealand) Limited is ultimately owned by PMI.

2 Reduced Risk Products, or RRPs, is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to those products than continued smoking.

3 I am based in Lausanne, Switzerland, and have been employed by PMI since 2006.

4 One of the RRPs PMI has developed is called *IQOS*. *IQOS* is an electronic device that heats a specially designed and manufactured tobacco product, marketed as *HEETS,* to generate an aerosol that the user inhales.

5 In this brief of evidence I explain:

5.1 why and how PMI developed *IQOS*;

5.2 the *IQOS* system; and

5.3 the research PMI has conducted that shows that, because *IQOS* does not burn tobacco, it produces far lower quantities of harmful and potentially harmful compounds than cigarettes.

6 I have been heavily involved in the research and development of *IQOS* and *HEETS* since 2005, when, as a consultant, I began helping PMI reorganise its industrial, business, and research and development processes to enable it to develop RRPs in a scientifically rigorous, robust, and transparent manner. In doing so, PMI sought to adopt an approach similar to how pharmaceutical companies develop drugs for regulatory approval. As I discuss in more detail in paragraphs 54 to 56 below, the years of rigorous testing behind *IQOS* and *HEETS* have enabled PMI to make two

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comprehensive applications for authorisation by the United States Food and Drug Administration (FDA). The first, a pre-market tobacco product application (PMTA), will allow the product to be marketed in the United States if PMI shows that the marketing of the product is "appropriate for the protection of public health" and the FDA issues a marketing order. In broad terms, the second application, called a Modified Risk Tobacco Product (MRTP) application, seeks authorisation to market *IQOS* as a product that presents less risk of harm than continued smoking.

7 I have read the High Court's code of conduct for expert witnesses, and agree to be bound by it. Although I work for PMI, wherever my evidence expresses an opinion about the science behind *IQOS* and *HEETS*, I give it impartially and objectively. All are within my area of expertise. I have also indicated those areas where further research will be necessary before a final conclusion can be drawn.

My background and qualifications

8 I am a scientist by profession. I have a BSc in Pharmacy and a PhD. in Pharmaceutical Sciences from the University of Strathclyde in Glasgow, Scotland. My thesis was on drug delivery systems for anti-cancer drugs. After completing my Doctorate in 1994, I worked for Cancer Research UK as the Assistant Director of its Phase I/II Clinical Trials Formulation Unit. In this role, I helped formulate and manufacture cancer drugs (including 'orphan' drugs - potentially promising drugs that have been abandoned by the pharmaceutical companies that developed them) for phase one and phase two clinical trials. In 1998, I took a position as Section Head of Manufacturing at Scherer Drug Delivery Systems, where I led the manufacturing of inhalable drugs for phase one and phase two clinical trials. In 1999, I became a consultant in PwC's Pharma Industry Practice (subsequently acquired by IBM Business Consulting Services in 2003). In that position, I advised pharmaceutical clients on how to modernise their industrial, business, and R&D processes in line with best practices, and in compliance with emerging global regulatory requirements.

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9 In 2005, I began working on a consulting project for PMI just as it was starting to invest substantially in research and development on RRPs, particularly with respect to PMI's then nascent heated tobacco technology, which I explain in more detail below.

10 In 2006, PMI hired me as its Director of Quality Management. In that role, I was responsible for developing programs to ensure PMI's research on RRPs met the highest scientific standards. Between 2008 and 2013, I held a variety of PMI positions relating to RRPs, including Director of Operational Excellence and Director of Next Generation Products. Throughout this time, I was heavily involved in the research and development of PMI's heated tobacco technology.

11 In 2013, I became the Director of Scientific Engagement for RRPs. In this role, I was responsible for engaging with the scientific community and other interested stakeholders regarding the provision of transparent access to information about our scientific research into RRPs. From the outset, PMI recognised there may be scepticism about our research and findings. The company decided the best way to address that scepticism would be to conduct our research in accordance with well-understood scientific standards, and to be entirely transparent about our research methods and results. This commitment to transparency involves making our scientific methodology, data, and results available for independent scrutiny. That way, external scientists and regulatory bodies are able to replicate, validate, attempt to disprove, question, or otherwise critique our studies, and/or conduct further independent research.

12 In January 2017, I assumed my position as Vice President, RRPs Corporate Affairs. In that role, I focussed on engaging with scientific, public health and other stakeholders on RRPs and the science behind them. I continued to be involved in PMI's scientific engagement efforts, although I had a broader portfolio of responsibilities that included engagement with medical professionals (led by a medical doctor on my team), a public policy group (that analyses such issues as potential unintended effects of the adoption of RRPs and how to address them), and communication.

13 In January 2018, I assumed my current position as Vice President, Scientific & Public Communications, where I focus on communication with the scientific community, regulators, public health stakeholders, and the wider public regarding RRPs.

The need to develop Reduced Risk Products

14 Cigarette smoking is addictive and dangerous. When someone lights a cigarette, the tobacco burns and creates smoke. More than 6,000 chemicals or 'smoke constituents' have been identified in cigarette smoke. Public-health authorities have classified approximately 100 of these constituents as causes, or potential causes, of smoking-related diseases. The harmful constituents include, among others, arsenic, benzene, benzo[a]pyrene, carbon monoxide, heavy metals (such as lead and cadmium), hydrogen cyanide, and tobacco-specific nitrosamines. The longer a person smokes, the greater the risk he or she will develop one or more serious illnesses as a consequence. Smokers are far more likely than non-smokers to develop heart disease, lung cancer, chronic obstructive pulmonary disease and other diseases.

15 Plainly, the best way to avoid the dangers associated with smoking is never to start, and for existing smokers the best way to reduce the risks is to stop completely. However, in reality, many smokers will continue to smoke despite the risks. The World Health Organisation estimates that more than a billion people worldwide will continue to smoke by 2025.[1] In developing its portfolio of RRPs, PMI is seeking to provide those who would otherwise keep smoking with less harmful alternatives.

Nicotine

16 Nicotine is one of the principal reasons why people smoke. While nicotine is addictive, it is not a primary cause of smoking-related

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1 Bilano V, Gilmour S, Moffiet T, d'Espaignet ET, Stevens GA, Commar A, Tuyl F, Hudson I, Shibuya K. (2015) Global trends and projections for tobacco use, 1990-2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control, Lancet 385-966-76.

diseases. It has not been shown to be carcinogenic,[2] or especially dangerous in the dose most smokers consume.

17 Pregnant women should not consume nicotine, as it causes constriction of blood vessels and increases heart rate. Similarly, in young people, nicotine may have a lasting impact on brain development (this effect has only been shown in animal studies, but it is enough to indicate nicotine should not be consumed by those under 18). For those suffering from cardiovascular disease, nicotine may worsen an existing condition. For most smokers, however, it is the cocktail of other chemicals in tobacco smoke that causes the greatest danger to their health.

The role of burning tobacco in health risk

18 Very few of the harmful chemicals in cigarette smoke are specific to tobacco; most are formed when any organic material is burned. While a few chemicals, such as tobacco-specific nitrosamines, are present only in tobacco, it is the act of burning the tobacco that leads to the formation of the majority of harmful chemicals.

19 The UK Royal College of Physicians (UK RCP) noted in 2016:[3]

> "Although the nature and extent of any long-term health hazard from inhaling nicotine remain uncertain, because there is no experience of such use other than from cigarettes, it is inherently unlikely that nicotine inhalation itself contributes significantly to the mortality or morbidity caused by smoking. The main culprit is smoke and, if nicotine could be delivered effectively and acceptably to smokers without smoke, most if not all of the harm of smoking could probably be avoided."

PMI's objectives in developing RRPs

20 To provide an alternative for people who would otherwise continue smoking cigarettes, PMI has set out to develop products that smokers find attractive, but which substantially reduce health risks by comparison with continued smoking. PMI has invested US$3 billion since 2008 in RRPs research and development alone. This sum does not include infrastructure, such as buildings, laboratories,

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2 See, for example, Haussmann H-J and Fariss MW. Comprehensive review of epidemiological and animal studies on the potential carcinogenic effects of nicotine per se. Critical Review in Toxicology, 2016; 46(8):701-734.

3 Royal College of Physicians, Nicotine without smoke, Tobacco harm reduction London: RCP, 2016

factories, and research and development centres. We employ more than 430 research and development experts in around 30 engineering and scientific disciplines, including over 300 highly-skilled scientists.

21 PMI's approach to research is inspired by long adopted practices of the pharmaceutical industry and FDA guidance, and follows international standards such as Good Laboratory Practices (GLP) and Good Clinical Practices (GCP).

22 PMI regards the task of its RRP programme – to develop and test alternatives that are less harmful than continued smoking – as a vitally important one. We see RRPs, like *IQOS* / *HEETS* and e-cigarettes, as a key part of helping communities move to being smoke free, and to giving smokers, who would otherwise continue to smoke, a less harmful option.

23 A successful RRP must be significantly less harmful than continued smoking. We seek to achieve this objective by developing products that substantially reduce the user's exposure to harmful chemicals. A successful RRP must also appeal as an alternative to cigarettes to smokers who would otherwise continue to smoke. No matter how much less harmful any new product is, it will be of no use if smokers do not like it, and will not switch to it. Experience has shown that smokers are most likely to switch to RRPs that successfully emulate the nicotine delivery, taste, sensory experience and ritual of cigarettes.

E-cigarettes

24 Many people are now familiar with e-cigarettes. E-cigarettes are a form of RRP, and the public health benefits of smokers switching completely from cigarettes to e-cigarettes are increasingly understood. At the same time as it continues to develop *IQOS*, PMI is developing e-cigarettes as part of its RRPs portfolio.

25 An e-cigarette is an electronic device that heats a liquid. The liquid often contains nicotine, propylene glycol, glycerine, and sometimes water, along with different flavours. Normally, there is a small metal coil that is heated, and the liquid that touches the coil is

vaporised. The liquid is heated to between 200 and 250 degrees, and produces a nicotine-infused vapour that the user inhales.

26 The key challenge for e-cigarettes is conversion (or complete switching). Even in countries where there has been a high take up of e-cigarettes, conversion rates remain relatively low. While e-cigarette technology continues to improve, and PMI supports e-cigarettes as another option for smokers who wish to move to a lower-risk alternative, many smokers do not appear to regard them as a satisfactory substitute for smoking.

IQOS* and *HEETS

27 The theory of heating rather than burning tobacco was first developed in the late 1980s. As I have already noted, it is the act of burning (or combustion of) the tobacco that leads to the generation of the majority of harmful chemicals found in cigarette smoke. The temperature at the tip of a burning cigarette can reach over 800°C and the heat released by the burning (combustion) process breaks down tobacco components generating smoke and ash. By contrast, if tobacco is heated – to temperatures of around 300°C – the process releases an aerosol instead of smoke. While the inhaled aerosol delivers nicotine to the user, the burning (or combustion) of the tobacco does not take place, and the aerosol that is generated contains significantly lower levels of harmful or potentially harmful constituents than cigarette smoke.

28 While the theory has been well understood for around 30 years, it is only in the last 10-12 years that the technology has developed to the point where a product like *IQOS* has become viable.

The IQOS system

29 *IQOS* is part of a system consisting of three major components:

29.1 A *HEETS* tobacco stick that contains a small plug of tobacco manufactured using a proprietary process, which is described more fully below. *HEETS* are designed for use only with the *IQOS* holder. When sufficient heat is applied, the tobacco in a *HEETS* stick generates a nicotine-containing aerosol.

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29.2 An *IQOS* electronic holder into which *HEETS* are inserted. The holder contains a heating element that, when switched on, heats the tobacco in the *HEETS* stick to form the aerosol a user inhales; and

29.3 An *IQOS* charger that re-charges the holder between uses and stores the holder between charges.

30 These components are illustrated below:

31 To make the tobacco component of the *HEETS* tobacco stick, high quality tobacco leaf is ground into a powder and mixed with glycerine, water, and binding compounds (like guar gum). This process creates a liquid paste, which is spread as a thin sheet and then put through a drying oven. The tobacco sheet is then crimped and made into a plug that is combined with other components to form the *HEETS* sticks used in the *IQOS* device.

32 The rest of the *HEETS* stick consists of a hollow acetate tube as well as a polymer film filter that allows the aerosol to cool. There is also a cellulose acetate mouthpiece filter. The filter components do not perform the same function as a filter in a cigarette. For example, the cellulose acetate mouthpiece is there to provide structural support for the lips of the user.

33 To operate *IQOS*:

33.1 The user inserts a *HEETS* stick into the holder, which results in the heating element (shaped like a blade) being inserted directly into the tobacco plug. The only part of the *HEETS* stick that remains outside the holder is the end containing the mouthpiece filter.

33.2 The user turns the device on by means of a button on the outside of the holder. The button, once pushed, initiates the heating element, which heats the tobacco in the *HEETS* stick.

33.3 Shortly after the heating element is turned on, the user can puff on the *HEETS* stick like he or she would with a cigarette.

33.4 As each puff is taken, the temperature of the tobacco decreases as fresh air is drawn through it. The heating blade "reads" this lower temperature and heats the tobacco ready for the next puff.

33.5 The holder shuts off after approximately six minutes or when 14 puffs have been taken on the *HEETS* stick, whichever comes first.

34 The average temperature of the heating element is carefully controlled throughout the process, in the range of 320°C to 350°C; and the heating element is automatically cut off if its temperature exceeds its set-point. While the average temperature of the element can reach no more than 350°C, the tobacco plug in the *HEETS* stick never gets this warm; its maximum temperature is around 320°C. At these temperatures, the tobacco never burns, and no smoke (by which I mean the collection of gases, vapour and airborne solids and liquid droplets generated by combustion) is produced.

35 While it does not burn, the tobacco in the *HEETS* stick close to the heating blade is subjected to a chemical process called torrefaction (or mild-pyrolysis). Pyrolysis is the term for the chemical decomposition of solid material caused solely by heating, but without combustion, and only occurs in the tobacco within a *HEETS* stick close to the heating element when heat from the *IQOS* device

is applied. The heat releases a nicotine-containing aerosol that the user inhales. The tobacco itself is not consumed to ash as is the tobacco in a lit cigarette. Rather, the tobacco remains intact in the *HEETS* stick. After the chemical change associated with heating, there is a change in colour of the tobacco close to the heating element and a lowering of the moisture level throughout the tobacco plug. A similar effect occurs when, for example, coffee beans are roasted.

36 The aerosol generated from the controlled heating of the tobacco in *HEETS* sticks contains gas and liquid droplets, but no solids. Cigarette smoke, by contrast, is made up of gas, liquid droplets and carbonaceous solid particles; these particles are like soot.

37 The gas and composition of the droplets in the aerosol are very different in their chemical makeup to the gas and droplets in cigarette smoke. While the gas and liquid droplets still contain harmful and potentially harmful chemicals, they are present at far lower levels than in cigarette smoke. Benzene and carbon monoxide, for example, which are among the most harmful smoking-related chemicals, are present in the *IQOS* aerosol at levels only 1-2% of what we find in cigarette smoke. While there are small quantities of up to three compounds in the aerosol that are not present in reference cigarette smoke, they have been studied carefully, and our research to date indicates they are not harmful.

Research into the risks associated with *IQOS* and *HEETS*

38 Before PMI released *IQOS* and *HEETS* into the market, we conducted extensive chemical and physical analysis of the aerosol together with in vitro and in vivo studies on the toxicity of *IQOS* vapour compared with cigarette smoke.

39 Our toxicological assessments involved standard toxicology, which was designed to help us understand whether the *IQOS* aerosol causes less damage to cells and organs than cigarette smoke. We also conducted extensive systems toxicology work. This research compares the effects of cigarette smoke and *IQOS* aerosol on organs and cells at the molecular level, with a focus on the mechanisms by which toxicants damage cells and cause disease.

40 Our chemical analysis studies showed that *IQOS* aerosol contains harmful chemicals at levels 90-95% lower than reference cigarette smoke, while our systems toxicology work shows a tenfold reduction in disease mechanism impact for cardiovascular disease and emphysema when compared with reference cigarette smoke. One study (an animal model of switching to *IQOS* including a smoking cessation group) showed a reduction in toxicity, a reduction in the disruption of mechanisms known to be associated with smoking-related disease, and a reduction in disease impact which was close to that for complete cessation.[4]

41 We have performed eight clinical studies to date on *IQOS*. Four looked at the absorption of nicotine, and the degree to which users found *IQOS* a satisfying substitute for cigarettes. These studies sought to assess the rate and amount of nicotine uptake in adult smokers using *IQOS* compared with that of cigarette smoking – this process is called pharmacokinetics. We also sought to understand how subjects feel after using the product, and in particular their urge to smoke again – this process is called pharmacodynamics. Both the pharmacokinetics and pharmacodynamics of an RRP should be similar to what happens when smokers use cigarettes to ensure they find it easier to switch, and do not revert back to cigarette use. These studies showed *IQOS* delivers nicotine with the same speed of absorption and in roughly the same maximum amounts as a standard cigarette.[5]

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[4] Phillips, B., E. Veljkovic, S. Boue, W. K. Schlage, G. Vuillaume, F. Martin, B. Titz, P. Leroy, A. Buettner, A. Elamin, A. Oviedo, M. Cabanski, E. Guedj, T. Schneider, M. Talikka, N. V. Ivanov, P. Vanscheeuwijck, M. C. Peitsch and J. Hoeng (2016). *An 8-month systems toxicology inhalation/cessation study in Apoe$^{-/-}$ mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with conventional cigarettes.* Toxicol Sci 149(2): 411-432. (@PMI Science) (PMID: 26609137) - doi:10.1093/toxsci/kfv243. Corrigendum: Toxicol Sci (2016) 151(2): 462-464. doi:10.1093/toxsci/kfw062

[5] See, e.g., Picavet, P., C. Haziza, N. Lama, R. Weitkunat and F. Lüdicke (2016). *Comparison of the pharmacokinetics of nicotine following single and ad libitum use of a Tobacco Heating System or combustible cigarettes.* Nicotine Tob Res 18(5): 557-563. (@PMI Science) (PMID: 26438645) - doi:10.1093/ntr/ntv220; Brossard P., Weitkunat R., Poux V., Lama N., Haziza C., Picavet P., Baker G., Lüdicke F. *Nicotine pharmacokinetic profiles of the Tobacco Heating System 2.2, cigarettes and nicotine gum in Japanese smokers.* Regul Toxicol Pharmacol. 2017 doi: 10.1016/j.yrtph.2017.07.032. [Epub ahead of print]; Haziza, C., G. de La Bourdonnaye, D. Skiada, J. Ancerewicz, G. Baker, P. Picavet and F. Lüdicke (2016). Evaluation of the Tobacco Heating System 2.2. Part 8: 5-Day randomized reduced

42 The second series of clinical studies were designed to show whether the levels of harmful and potentially harmful chemicals in the *IQOS* aerosol are significantly lower in adult smokers using *IQOS* exclusively compared to those smoking cigarettes.

43 We selected 15 biomarkers of exposure to harmful chemicals, which can be quantified reliably in either blood or urine of study participants. The key criteria for selecting these biomarkers are that they are specific to smoking (in other words they do not accumulate in the body in large quantities through other activities), their presence in the body is reversible when people stop smoking, they include compounds present in both the gas and particulate components of cigarette smoke, they are implicated in toxicity affecting different organs (they include, for example, chemicals which affect both the lungs and the heart), and they can be reliably quantified with validated methods.

44 During clinical studies, smokers were split into three groups: one which continued to use cigarettes, one which stopped smoking for the duration of the study, and one group that switched to *IQOS*.

45 We conducted four trials where smokers were divided into these three groups. Two were "confinement" studies, where all participants remained in a clinic and were monitored over five days. The other two were "ambulatory" studies, where the subjects went home after five days of confinement and continued to be monitored over the next 85 days. The focus of the research was the effect switching to *IQOS* had on the 15 biomarkers of exposure when compared with people who continued to smoke, and with those who stopped altogether.

46 The results of both the "confinement" and "ambulatory" studies were clear, and significant. Those who switched to *IQOS* showed

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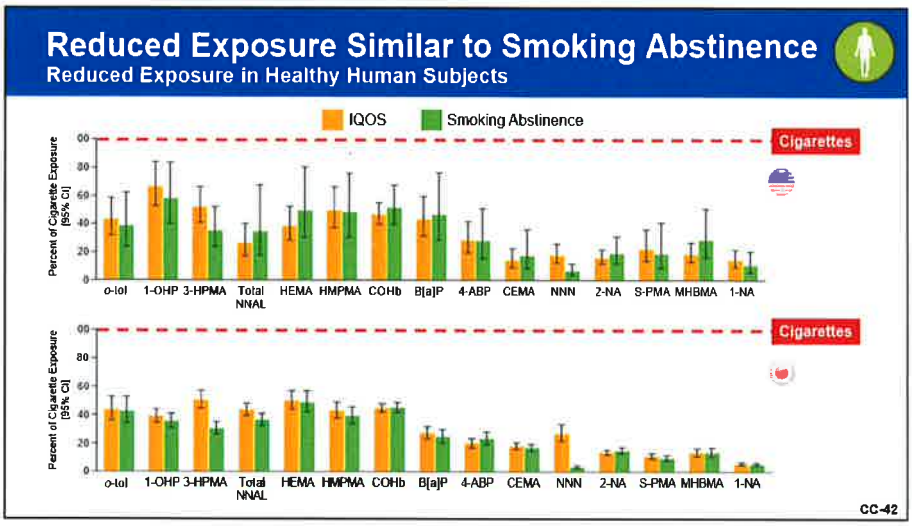
exposure clinical study in Poland. Regul Toxicol Pharmacol 81 Suppl 2: S139-S150. (@PMI Science) (PMID: 27816672) - doi:10.1016/j.yrtph.2016.11.003

levels of absorption of harmful chemicals that closely approached those who stopped smoking altogether.



47 These 90-day studies also looked at six clinical risk endpoints, such as oxidative stress, inflammation and airway function, that are known to be affected by smoking and reverse upon cessation within a 3-month time frame. The endpoints are used to determine if the reduction in exposure to harmful chemicals translates into changes in short term clinical risk factors known to be associated with smoking-related diseases. Seven additional markers were measured to monitor the safety of the subjects.

48 The changes in clinical risk endpoints that we measured in smokers who abstained for the duration of the studies were small, which was to be expected in a healthy study population, but their direction was consistent with the literature on cessation, and the magnitude of the changes was clinically significant. In both 90-day studies, we observed that switching to *IQOS* also led to positive changes in clinical risk endpoints compared with continued smoking. The changes after switching to *IQOS* were consistent with the direction of change expected from cessation and were of a similar magnitude to the changes we observed in the participants who abstained from smoking. Longer-term studies are underway.

49 Our key conclusion, both from our laboratory research and our clinical trials in which biomarkers are monitored, is that smokers

who switch completely to *IQOS / HEETS* achieve a level of reduction in their exposure to harmful and potentially harmful chemicals close to the reductions achieved by people who stop smoking altogether.[6]

50 Independent studies into *IQOS / HEETS* have produced findings largely consistent with our internal studies. An exploratory study by a leading Ukrainian research institute, and published in the periodical Ukrainian Health, confirmed improvements in biomarkers in line with our own studies,[7] and research by cardiologist and e-cigarette researcher Dr K. Farsalinos, expected to be published later this year, included the following findings:

50.1 Measured harmful constituents are largely in line with PMI's own research; and

50.2 *IQOS* is a harm reduction option.[8]

51 The United Kingdom's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, an independent body which advises the Food Standards Agency, the Department of Health and other United Kingdom Government Agencies, recently investigated heat not burn tobacco products. It released its findings on 12 December 2017. The Committee found that heat not burn products pose some risk to public health, but concluded that the exposure to compounds of concern is reduced by 50-90% compared to that from conventional cigarette smoke. It noted that complete cessation remains the best option for smokers, but that switching to heat not burn tobacco products is likely to pose a lower risk to overall health than continued smoking. The Committee also noted

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6 Luedicke F, Picavet P, Baker G, Haziza C, Poux V, Lama N and Weitkunat R (2017). Effects of switching to the Menthol Tobacco Heating System 2.2, *Smoking Abstinence of Continuing Cigarettes on Biomarkers of Exposure: A randomized controlled, open-label, multicentre study in sequential confinement and ambulatory settings (Part 1).* Nicotine and Tobacco Research, e-pub ahead of print (PMID: 28177489).

7 *Evaluation of electronic nicotine delivery system (ENDS) effects on cardiovascular disease risk, based on endothelium function as factor of its determination*. Ye.A. Kvasha, O.V. Sribnaya, I.P. Smirnova, I.V. Tretyak, A.A. Boroday SE, National Scientific Centre "M.D. Strazhesko Institute of Cardiology, Mas of Ukraine", Kiev, Ukrainian Health, 18 July 2017

8 https://gfn.net/co/downloads/Presentations_2017_/Dr%20Konstantinos%20Farsalinos.pdf

that a reduction in the risk to bystanders would be expected where smokers switch to heat not burn products.[9]

52 A further PMI clinical study is presently underway with close to 1000 participants. This study is examining clinical risk endpoints after both six and twelve months.

53 PMI is always looking at ways the product can be improved further, and we are constantly monitoring the performance of the device and the way users are responding to it. We will continue to conduct studies on the product and have an extensive surveillance programme in place in those markets where *IQOS* and *HEETS* are well established.

Regulatory engagement

54 PMI (through its affiliate, Philip Morris Products S.A.) is currently seeking two regulatory authorisations for *IQOS* with the United States Food and Drug Administration (FDA). In the first, called a Premarket Tobacco Product Application (PMTA), PMI seeks authorisation to market *IQOS* and *HEETS* in the United States as a "new tobacco product" without any statements regarding reduction in health risks relative to continued cigarette smoking. To gain approval, PMI must demonstrate the product is "appropriate for the protection of public health", taking into account the risks and benefits of the product to the population as a whole.

55 In the second application, PMI seeks authorisation to market *IQOS* as a modified risk tobacco product (MRTP). PMI is seeking regulatory authorisation to make three claims, namely that:

55.1 switching completely from cigarettes to the *IQOS* system can reduce the risks of tobacco-related diseases;

55.2 that switching completely to *IQOS* presents less risk of harm than continuing to smoke cigarettes; and

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[9] Committees on Toxicity, Carcinogenicity and Mutagency of Chemicals in Food, Consumer Products and the Environment (COT, COC and COM): Toxicological evaluation of novel heat-not-burn tobacco products – non technical summary, COT 2017/04; December 2017, at [27] and [29]

55.3 that switching completely from cigarettes to the *IQOS* system significantly reduces a smoker's exposure to harmful and potentially harmful chemicals.

56 On 25 January 2018, the Tobacco Product Scientific Advisory Committee (TPSAC), a nine-member committee that advises the FDA, provided its advice to the FDA on some aspects of the MRTP application. The Committee accepted the proposition in paragraph 55.3 by eight votes to one, but rejected the propositions in paragraphs 55.1 and 55.2 (by eight votes to one and five votes to four respectively). Committee members indicated they were open to revisiting the propositions in those paragraphs once evidence is available to show that the reduction in exposure to harmful and potentially harmful compounds translates into improved health outcomes. While TPSAC's opinion is not binding on the FDA, it represents one step in the MRTPA review process, which is ongoing. It does not affect the PMTA application.

Air quality

57 A clinical study to determine the impact of *IQOS* aerosol on nearby non-users is underway but has not yet been completed. That said, we have conducted extensive indoor air quality research. Our study looked at 18 markers of air quality associated with cigarette smoke, including carbon monoxide, benzene, and nitrous oxide. We measured the background levels in the room, then tested the levels associated with cigarette smoke and *IQOS* aerosol.[10] Unsurprisingly, exposing the room to cigarette smoke resulted in much higher levels of harmful chemicals in the air. After *HEETS* were consumed, however, only two of the 18 markers could be detected. These were nicotine, at a level 250 times lower than European Union indoor occupational air quality standards,[11] and

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[10] Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality, Mitova and others, Regulatory Toxicology and Pharmacology, Vol 80, October 2016, pp 91-101

[11] European Agency for Safety and Health at Work: Directive 2006/15/EC

acetaldehyde at a level 40 times lower than European Union indoor exposure limits.[12]

58 We are currently conducting a detailed study in Japan, where indoor smoking and indoor *IQOS* use are common.

Conversion rates

59 As I have said, conversion rates for e-cigarettes remain relatively low. Conversion rates for *IQOS* – by which we mean users who go from smoking cigarettes to using *IQOS / HEETS* for at least 95% of their daily tobacco consumption – have been significantly higher.

60 PMI's affiliates began selling *IQOS* in pilot markets (Nagoya and Milan), then began selling *IQOS* nationwide in Japan in April 2016. By June 2017, consumer purchases of *IQOS* and *HEETS* represented 12.7% of all tobacco products sold in Japan. PMI is now selling *IQOS* in key cities in more than 31 countries. In Japan, the conversion rate for *IQOS* is around 72% – in other words, around 72% of smokers who go through a guided trial and purchase *IQOS* switch to it completely. Other major markets show complete conversion rates of at least 54%.

61 Worldwide, over 3.7 million adult consumers have stopped smoking and completely switched to *IQOS*, despite *IQOS* being available in most markets for less than two years. Further, our data shows that once an adult smoker converts to *IQOS*, he or she is very unlikely to switch back to cigarettes – depending on the country, only 1-4% of fully converted users switch back to smoking.

Appeal to non-smokers

62 PMI is acutely aware of the risk that a new product like *IQOS* might provide an additional pathway to nicotine use for those who have never smoked, and those who have given up. PMI tries hard to discourage non-smokers from taking up *IQOS* in all its markets, and we closely monitor this factor as part of our post-market surveillance. In studies over the two years the product has been

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[12] The Index Project, Critical Appraisal of the Setting and Implementation of indoor exposure limits in the EU, EC, Joint Research Centre, Institute for Health and Consumer Protection, January 2005

widely available, the evidence continues to show it has very low appeal to those who have never smoked or who have given up. Fewer than 5% of customers are former smokers who had given up, and even fewer (less than 3%) had never smoked before taking up *IQOS*.

Conclusions

63 My principal conclusion, based on the totality of the scientific evidence, is that a smoker who switches completely to *IQOS* will be exposed to less risk of harm than one who keeps smoking. At every level of research, the results are clear. The moment a smoker stops burning tobacco, the reduction in exposure to harmful and potentially harmful compounds is substantial.

64 No new product of this kind, including any e-cigarette, has gone through as much scientific analysis as *IQOS*. And, as noted above, for a Reduced Risk Product to be effective, it must be appealing enough to smokers that they want to switch to it completely. To date, *IQOS* performs far better than any e-cigarette by this measure.

65 Finally, and most critically, removing *IQOS* from any market where it has started to gain a foothold will force many former smokers, who have already switched to *IQOS*, to return to a far more harmful product, with all the attendant risks to the smokers themselves, and ongoing detriment to public health.

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