Philip Morris's Population Health Impact Model Based on Questionable Assumptions and Insufficient Health Impact Measures Does Not Adequately Support its MRTP Application

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To be granted an MRTP order under section 911(g) of the Family Smoking Prevention and Tobacco Control Act, Philip Morris (PM) must demonstrate that the marketing of its IQOS product will or is expected "to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." For its modified exposure claim, PM must further demonstrate that issuance of an exposure modification order would be "appropriate to promote the public health." Therefore, FDA recommends that an MRTP application should contain *"an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality in the population as a whole."* In particular, FDA recommends that applicants submit "quantitative estimates of the effect the marketing of the product, as proposed, may have on the health of the population as a whole." (Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, page 21). In an effort to meet this requirement, PM created its "Population Health Impact Model" (PHIM), a computational model that purports to estimate the potential impact on public health of marketing its IQOS as an MRTP.

However, PM has not met its burden to demonstrate that a MRTP order would "benefit the health of the population as a whole" or "promote the public health" because its PHIM makes several questionable assumptions, leaves out some important measures of health impact, and relies heavily on research funded by the tobacco industry. It ignores risks to individuals other than the product user, compares risks only to those of cigarettes, focuses on deaths from only 4 diseases, ignores nonfatal disease incidence, ignores healthcare costs, and makes a number of other questionable assumptions. Our detailed comments on each of these issues follow.

Risk to others is ignored. The PHIM model uses individual risk times prevalence to derive population harms. It ignores risk to others, such as secondhand exposure from IQOS products. PM alleges that "we [PM] do not account for environmental tobacco smoke exposure, where we showed earlier (Weitkunat 2015)[1] that, whether or not the MRTP reduces the risk from ETS exposure would have little effect on the estimated drop in mortality associated with MRTP introduction" (Module 6, Section 6.5.5, page 41). The work cited was funded by the tobacco industry, and needs to be verified in independent work. It is also unclear what the authors mean, given that it is known that secondhand smoke exposure from cigarettes results in over 42,000 deaths a year in the US alone.[2] It seems likely that IQOS products would also cause mortality in non-users who are exposed.

Reduced risk compared to what? The PHIM considers only 5 tobacco use behaviors – never smoking, current cigarette smoking, current MRTP use, current dual use (MRTP and cigarettes), and former use (of cigarettes or MRTP or dual use of cigarettes and MRTP). The model ignores other tobacco products, such as e-cigarettes, which PM and other tobacco interests consistently argue have substantially lower risk of illness and death than cigarettes. Thus, the comparison in PM's analysis is only between a higher risk product (cigarettes) and what PM claims is a lower risk product (its IQOS Tobacco Heating System or "THS"). The results would be very different if the comparison were with a lower risk product (e-cigarettes), and it is likely that some e-cig users would be lured to heat-not-burn (HNB) products, suggesting that such a comparison is reasonable. PM acknowledges that

> "the Prevalence Component only accounts for the use of cigarettes and an MRTP, and does not consider other tobacco products, such as cigars, pipes or smokeless tobacco. Failure to do so might cause some bias in estimating the reduction in deaths attributable to an MRTP if CC smokers switching to an MRTP tend to change their use of these other products. However, unless evidence emerges that this occurs to any material extent, no attempt will be made to account for this possibility, as this would make the estimation process extremely complex and highly unreliable due to the number of assumptions required and the interactions between the smoking statuses."

While we acknowledge that data on the risks of products such as e-cigarettes are only now becoming available, there have been studies on the risks associated with cigar use and smokeless tobacco use. PM is willing to assume that the relative risks of death from use of IQOS is a fraction of the risks of death from cigarette smoking. They could easily conduct a sensitivity analysis by assuming the relative risk of death from e-cigarette smoking is a fraction of the risk from cigarette smoking, using reasonable estimates of the risk ratio.

It is not acceptable for PM to say that there is no evidence that switching from products other than cigarettes might occur. Evidence is available from other countries and for products that may be similar to IQOS. In Japan, where IQOS products are now available, over one-third of IQOS users are poly-users, most of whom also smoke cigarettes.[3] Our analyses of the 2012-2014 National Adult Tobacco Surveys indicate that 80.9% of e-cigarette users are poly-users, most of whom also smoke cigarettes. Thus, the behavior of IQOS users, including poly-use with conventional cigarettes and other tobacco products, can be included in modeling the impact of this new product on health.

The PHIM assumes cigarette users will switch to IQOS use exclusively. The model assumes zero probability that the user will switch to cigarettes or become a dual user of cigarettes and IQOS (Module 6, Section 6.5.3.4, page 25). This is not a reasonable assumption. As described above, we already have contrary evidence from IQOS use in Japan and from e-cigarette use in the U.S. Poly-tobacco use, the use of 2 or more tobacco products, is common, and was reported by 3.9% of the adult population in 2015.[4] There is a growing and substantial literature showing that those who initiate tobacco use with e-cigarettes may go on to smoke cigarettes,[5] and that those who use e-cigarettes remain dual users rather than quitting conventional cigarettes.[6] IQOS is likely to have a similar impact.

The PHIM includes only deaths, ignoring disease incidence. However, to be granted an MRTP order, section 911(g)(2)(B)(ii) requires PM to demonstrate that the "reasonably likely overall impact of use of [IQOS] remains a *substantial and measurable reduction in overall **morbidity*** and mortality among individual tobacco users." While smoking causes nearly 500,000 deaths a year in the US,[7] the morbidity burden is much larger, with 6.9 million US adults reporting smoking-related diseases in 2009.[8] Asthma, for example, a disease known to be exacerbated by smoking, impacted 18.4 million US adults in 2014 and caused 3,651 deaths.[9] Ignoring disease morbidity resulting from IQOS use grossly underestimates its impact on health.

Only 4 diseases are included in the PHIM. The model considers only 4 diseases caused by smoking – lung cancer, ischemic heart disease (IHD), stroke, and chronic obstructive pulmonary disease (COPD). PM acknowledges that "overall estimates of deaths saved due to the introduction of IQOS would have to be increased about 50% to give an estimate for all smoking-related diseases combined" (Module 6, Section 6.5.5, p. 41). This makes it clear that the estimate provided of deaths is a gross underestimate. At least 22 causes of death for adults[10] and 4 causes of death for infants[11] have been causally linked to cigarette smoking. Studies need to be conducted to investigate whether there are other diseases that may be associated with IQOS products.

Relative risk estimates are all derived from studies funded by Philip Morris, but better estimates are available. All the studies cited for the excess relative risk estimates are conducted by Peter N Lee and colleagues, British researchers at a private consulting firm (P N Lee Statistics and Computing Ltd) that is funded by Phillip Morris. Many of these studies are published in the journal *Regulatory Toxicology and Pharmacology*, a journal recently found to show bias in favor of the tobacco industry, publishing mostly work funded by the industry and reaching conclusions that favor the industry in 96% of papers.[12] The PHIM uses relative risk (RR) of death for cigarette smokers relative to never cigarette smokers from 4 smoking-related diseases (lung cancer, IHD, stroke, and COPD). However, rather than use the estimates published by the Surgeon General of the US,[7] they rely on estimates from a published meta-analysis by Forey and colleagues[13] involving 39 North American studies (see Module 6, Section 6.5.3.5, page 28) while the 2014 US Surgeon General Report's[7] RR estimates were based on US cohorts (See Module 6, Section 6.5.3.5, Table 7, and Module 6, Section 6.5.6, page 44). PM claims that their RR estimates are better. However, the PM estimates come from a study funded by Philip Morris and conducted by Lee and colleagues. The PHIM model needs to be based on findings from independent research that is not funded by the tobacco industry. ***The Surgeon General estimates, which are larger and independently vetted through a more thorough process of independent peer review than the Forey estimates, are more appropriate and should be used in all analyses.***

The PHIM assumes that the Relative Risk (RR) of death from IQOS is a fraction of the RR of death from cigarette smoking. Because the RR of death caused by the 4 smoking-related diseases for users is not known, the authors replied upon a "fraction" measure called "the relative exposure of IQOS compared to smoking cigarettes", denoted by "*f*" (see page 6, Table 5 on page 19, and pages 22-23). They developed some clinical and non-clinical models, and estimated that the mean value of "*f*" is 0.35 and the median value is 0.30. Afterwards, in their simulations, they used *f* -values between 0.1 and 0.3. ***This is a KEY assumption used in their***

approach: whatever the RR value of cigarette smoking for death, they multiplied that RR value by the f -value (0.1 to 0.3). As a result, the use of the MRTP yields far fewer attributable deaths compared to cigarette smoking. The validity of this assumption needs to be investigated by independent researchers. PM also cites an industry funded study by Weitkunat[1] (Module 6, Section 6.5.1, page 6).

Moreover, with a single exception, the clinical results included in the MRTP application do not show statistically significant improvements in the biomarkers of harm that PM assessed in actual people. Thus, even when taken uncritically at face value, PM's own application does not support assertions of reduced harm, much less the 70% to 90% reductions in risk that their model assumes.[14]

The RR of death for dual use is arbitrarily assumed to be the mean of the risk of cigarette smoking plus the risk of IQOS use (see Module 6, Section 6.5.3.2, page 19, Table 5). The basis for this assumption seems unclear and this approach is highly simplified. There is some evidence that dual users have greater risks of negative health outcomes than sole cigarette users,[15, 16] which suggests that the PHIM model would lead to an underestimate in the number of deaths attributable to use of cigarettes and IQOS.

The PHIM model doesn't consider the impact that IQOS product use might have on people with pre-existing conditions. Cigarette smoking and e-cigarette use among people with cardiovascular disease (CVD) or respiratory diseases have been shown to worsen their health outcomes and increase their healthcare costs.[7, 17] One study reported that ongoing tobacco use was associated with worsened ischemic conditions.[18] Another study found that patients with peripheral artery disease who smoked were more likely to be hospitalized, and had higher annual healthcare costs, than those who didn't smoke.[19] It is likely that IQOS use would have a similar negative impact on those whose health is already compromised.

E-cigarettes, a product with lower disease risks than cigarettes, have been found to have additional independent negative health impacts even among cigarette smokers. We compared the prevalence of symptoms among adult users and nonusers of e-cigarette users. Even after controlling for cigarettes smoked per day, e-cigarette users had greater odds of symptoms including wheezing and shortness of breath.[15] PM needs to present data that the IQOS aerosol is different enough from e-cigarettes to avoid these effects or include them in its models. And PM also needs to determine whether there are other health effects associated with IQOS use.

The PHIM completely ignores healthcare costs. One way of quantifying the impact of illness is through healthcare costs. Cost measures incorporate the severity and time course of illness. There are many published studies that document methods for estimating healthcare costs attributable to tobacco use.[20-25] ***Ignoring healthcare costs is a major flaw in the PHIM and a major omission in this MRTP application.***

The PHIM completely ignores possible health impacts of IQOS use on young adults. Related to the point above (omission of health care effects not related to fatal diseases), the model ignores health effects of increased use of e-cigarettes and cigarette smoking among young adults. Research has found substantial increase in utilization of hospital services (for

reasons other than pregnancy or injury) in young adult smokers, including those in their 20s.[26] The MRTP application assumes there are no health effects in the population under 30. Youth and young adults who use products may suffer health effects, experience premature mortality, and incur healthcare costs. ***Leaving young people out of the model will lead to an underestimate of the impact of IQOS use on health.***

The PHIM completely ignores any health impact of use on children. Children are likely to be impacted by the product in several ways. First, children are likely to suffer negative health effects when exposed to their parents' secondhand smoke.[27-29] A recent literature review identified a number of toxic compounds in e-cigarette aerosol in addition to particulate matter, indicating that the aerosol can be harmful to human health.[30] Thus, the vapor from IQOS is likely to be harmful as well and should be investigated. Second, women who use IQOS while pregnant may cause lifelong health impacts for their children, as is known to be the case for women who smoke cigarettes or use snuff while pregnant.[31-33] Other risks to children from IQOS use include fires and explosions, such as those that occur with e-cigarettes, and nicotine poisoning from the product such as the poisoning that has occurred from e-liquids.

The PHIM completely ignores any impact of IQOS use on uptake of cigarette smoking by youth and young adults. If IQOS products are marketed as a MRTP, this may impact tobacco use initiation among youth and young adults who would never initiate tobacco use if the IQOS product is never allowed in the market. Youth have initiated tobacco use with e-cigarettes at unprecedented rates,[34] and may find the IQOS product to be similarly appealing. The PHIM application assumes that uptake of the MRTP will be limited among youth because of the relatively high cost. However, this assumption ignores shared use among users, as occurs with cigarettes and hookah. There is consistent and strong evidence that e-cigarette use among adolescents and young adults increases subsequent uptake of cigarette smoking.[5] One of the claims about IQOS in this application is that IQOS mimics cigarette smoking better than e-cigarettes or vaping because of more rapid nicotine delivery. Therefore, even if the rate of purchase of the IQOS is lower among youth than cheaper cigarettes, e-cigarettes or vaping devices, IQOS may be much more effective at addicting youth and young adults to nicotine as well as increasing transition to cigarette smoking among youth who experiment with shared devices. A net increase in nicotine addiction and cigarette uptake among adolescents and young adults is a realistic possibility that this application ignores.

Conclusion: The Population Health Impact Model underestimates the health impact of IQOS products and the model predictions do not justify the MRTP claim. The model does not meet the FDA's recommendation for MRTP applications that they contain *"an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality in the population as a whole"* (Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, page 21). In Philip Morris' own words, the "PHIM has been developed to estimate the reduction in mortality from the four major smoking-related diseases (lung cancer, IHD, stroke and COPD) that would occur over a period following the introduction of a MRTP" (Module 7, Section 7.4, page 1). This is contrary to the requirement that the application consider morbidity and mortality and the population as a whole. The model omits many important factors, including morbidity impacts, healthcare

costs, risks to nonusers, impact on children, mortality from diseases other than the 4 considered, impacts on people with pre-existing conditions, and likely dual- and poly-use patterns. The analyses presented compare IQOS to cigarette smoking, while many users are likely to be e-cigarette and other tobacco product users, resulting in a very different change in risk.

PM's so-called Population Health Impact Model greatly underestimates the impact of IQOS products on the market and does not show a positive impact on the health of the population as a whole. The application should be denied.

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