

Detailed analysis of the Executive Summary (Section 2.7) submitted by Philip Morris International in support of its MRTP application for IQOS

Stanton A. Glantz, Ph.D. and Lauren K. Lempert, JD, MPH
UCSF Tobacco Center of Regulatory Science

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This comment is a detailed analysis of the Executive Summary of Philip Morris International's application, including commentary on specific statements in the Executive Summary. For detailed discussion of these issues, including relevant references, see the public comments that the UCSF TCORS has submitted.¹

While there are many issues raised in the Executive Summary Philip Morris International (PMI) submitted, there are four overarching problems that represent fatal flaws in the application:

- The application completely ignores anyone under the legal age to purchase tobacco products. Section 911 of the Family Smoking Prevention and Tobacco Control Act requires MRTP applicants to submit, and FDA to consider, scientific evidence of how the product affects nonusers, which includes kids. Based on the experience of e-cigarettes, it is highly likely that IQOS products will appeal to kids and create or increase their nicotine addiction. And based on the experience with e-cigarettes, many of these kids will go on to use conventional cigarettes. Even if they do not, adopting the IQOS product will have adverse health effects on youth.
- The health risk assessment aspects of the application assume 100% switching from conventional cigarettes to IQOS, despite the fact that PMI's own data on use patterns, both in their experimental studies and population monitoring in other countries, show substantial levels of dual use. Section 911 requires MRTP applicants to demonstrate that their product "as it is actually used by consumers" will reduce harm and risk of diseases to individual users and benefit the the health of the population as a whole. An accurate assessment of health effects therefore needs to assess dual use of IQOS and other tobacco products, including not only conventional cigarettes but also e-cigarettes and smokeless tobacco products since dual and poly use is an increasingly common pattern. This is another area where the experience with e-cigarettes is likely informative, because, while optimists may assume that the primary effect of e-cigarettes would be conventional cigarette smokers switching to them, the dominant use pattern remains dual use.
- While the aerosol chemistry, in vitro studies, and animal toxicology consistently show lower levels of adverse biological effects, the human studies do not show statistically significant differences between IQOS and conventional cigarettes for most of the biomarkers of potential harm. Because the human studies are closest to the real world, they deserve the

¹ <https://tobacco.ucsf.edu/list-public-comments-fda-and-other-agencies-ucsf-faculty-and-fellows-and-others-links-comments>

heaviest weight and do not support the claims of reduced risk. It is not at all unusual for a particular intervention to show an effect in vitro or even in animal models, yet not be effective in humans. This appears to be the case with IQOS.

- The evidence presented on warning labels shows that they are likely to be misunderstood and lead people to underestimate the risks associated with using IQOS. This is a particular problem with the reduced exposure claims because they will be misunderstood as reduced risk claims.

Following is a more detailed analysis of the Executive Summary with page references:

Page 10, paragraph 3: “For a smoker who switches to THS from cigarettes, this reduction in exposure to toxicants provides the foundation for the reduced harm rationale for this product as an MRTP.” This statement and variants of it permeate the application, creating a very strong assumption that is not supported by the data PMI presents on actual use patterns, which show high levels of dual use. While there is nothing wrong with PMI assessing the effect of completely switching to IQOS, an accurate assessment of the individual and population health impacts of the new product require also studying dual use.

This is a very important point because for FDA to issue an MRTP marketing order, PMI must have demonstrated substantial evidence to support its claim that users are not misled by any labeling or advertising that purportedly warns consumers that they will not get the claimed reduction in harm unless they completely switch from all other tobacco products (including but not limited to conventional cigarettes, cigars, hookah, and e-cigarettes) to IQOS.

Considering dual use is important because emerging evidence from e-cigarettes shows that dual use of e-cigarettes and conventional cigarettes is more dangerous than using either product alone. This is true despite the fact that e-cigarettes have an overall lower toxic burden than conventional cigarettes.

Considering the likelihood of dual use is also important in assessing the warning messages and consumer education. The research that PMI summarizes here does not address that question at all.

Page 11, paragraph 4: “The first step in the assessment program was the chemical characterization of the aerosol generated by THS, which confirmed that THS aerosol contains substantially reduced levels of HPHCs (~90% overall reduction) compared with CC smoke.” Here and in many other places in the application, we see this statement that IQOS reduces HPHCs by 90%. While this is what the data Philip Morris presents shows, there is already at least one independent study (Auer R, et al. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. *JAMA Intern Med.* 2017;177(7):1050-1052. doi:10.1001/jamainternmed.2017.1419) that shows substantially higher levels of toxins than Philip Morris reports.

Page 12, last three paragraphs: This is another place where the application explicitly limits itself to the effects of *complete switching* from conventional cigarettes to IQOS. This is an incomplete analysis of the likely effects of the new product.

Page 13, paragraph 2: Here PMI accurately states the legal requirement that the IQOS be assessed “as it is actually used by consumers,” yet their analysis assumes that all IQOS consumers will completely switch from conventional cigarettes. This assumption is inconsistent with the data actually shown in the application.

Page 14, paragraph 4: PMI explicitly notes, albeit obliquely, that dual use exists when they say: “Furthermore, an actual use study showed that after 6 weeks, approximately 15% of the study participants had switched from cigarettes to either exclusive *or predominant use* of THS.” The “predominant users” are dual users, not people who switched completely.

Page 18, paragraph 1: Here PMI repeats the mantra that “‘nicotine itself is not a highly hazardous drug’ and that ‘most of the harm caused by smoking arises not from nicotine, but from other components of tobacco smoke’” (this time from the UK Royal College of Physicians). This statement, while accepted uncritically in some circles, ignores the many, many harmful effects of nicotine beyond addiction, including promotion of cancer, lung disease and heart disease through its effect on the nicotinic acetylcholine receptors as well as adverse effects on pregnancy and the developing fetus. Saying that nicotine is not the most dangerous thing in cigarette smoke does not mean that it is without risk.

And of course, addiction risk itself is a problem, especially if it leads to non-users initiating with IQOS, as well as IQOS serving as gateway to cigarettes . PMI also ignores risk of nicotine poisoning with kids akin to nicotine poisoning risk to kids and infants by e-cigarettes.

Page 18, paragraph 2: “An important corollary of achieving population harm reduction with MRTPs is that consumers will actually use them, *ideally* replacing the use of more harmful products with products that significantly reduce the exposure to toxic compounds, thus reducing harm and the risk of tobacco-related disease [emphasis added].” This is another of the many places in which PMI builds the application on the assumption, unsupported by PMI’s own data, that the dominant behavior will be complete substitution.

Moreover, looking at the marketing (and just thinking about profit maximization) strongly suggests that PMI wants *new* users as well as switchers. That’s why they have the slick Apple-like design of products and stores – to attract new young adults certainly, and probably teens and kids too (who always want to imitate older siblings)

Page 18, paragraph 2: “... These products should not attract persons who do not currently use tobacco products, i.e., never smokers or former smokers.” This statement is based on the strong implicit assumption in the whole analysis that IQOS *won’t* attract never smokers or former smokers. The experience with e-cigarettes certainly violates this assumption. Indeed, some of PMI’s own data indicates that some never and former smoker adults will be attracted to the product. While one could theoretically argue that these people would have relapsed to smoking cigarettes anyway, no evidence is presented to support such an argument.

Page 19, paragraph 1: This is another place where the assumption is made that IQOS will not attract never smokers or negatively impact the intention of smokers to quit. Again, the experience of e-cigarettes seriously calls into question this assumption which is never tested in the application.

Page 19, second bullet: The same assumption is applied again in a different context.

Page 20, bulleted list: Ultrafine particles are missing from this list. They are a major actor in creating many of the adverse cardiovascular and pulmonary effects of smoking and e-cigarettes (and likely the IQOS product) because the key way that IQOS works is by delivering an aerosol of ultrafine particles and nicotine, similar to cigarettes and e-cigarettes.

Page 20, paragraph 4: The analysis is completely limited to HPHCs that have been identified in cigarette smoke. Given that the IQOS HeatSticks are manufactured using a different process than cigarettes, there is a very good chance that it will have a different toxic profile than cigarettes and deliver different compounds. There is no assessment of any potential unique exposures generated by the IQOS.

Page 24, paragraph 1: “Second, it is acknowledged that product-specific epidemiological evidence is not available...” Philip Morris makes the point that there is no specific epidemiological evidence related to IQOS, but information from e-cigarettes would be relevant and should be discussed in the application.

Page 24, paragraph 1: “The assessment of the candidate MRTP therefore needs to address this complexity by demonstrating through a broad array of indicators that — *compared with smoking* — the use of a candidate MRTP leads to a significant reduction in exposure to HPHCs, which in turn leads to a significantly reduced impact on mechanisms leading to tobacco-related diseases [emphasis added].” Why is the comparison limited to smoking? PMI (and FDA) should be comparing IQOS to similar alleged “reduced harm” products like e-cigarettes and smokeless tobacco. In determining whether to issue a MRTP order, section 911(g)(2)(B) requires FDA to find that “the product as actually used by consumers will not expose them to higher levels of other harmful substances *compared to the similar types of tobacco products then on the market...* [emphasis added].” (FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, March 2012, p. 4) E-cigarettes are a “similar type of tobacco product” currently on the market, and are certainly more similar than conventional cigarettes to IQOS HeatSticks. Like e-cigarettes, the subject IQOS HeatSticks are electronically heated using batteries that are charged using a USB power adaptor. Smokeless tobacco may also be considered a “similar type of tobacco product” since many manufacturers and advocates consider and market smokeless products as “reduced harm.”

Additionally, FDA is required to evaluate the benefit of the MRTP candidate product to the health of individuals and to the population as a whole. In evaluating this, FDA is required by section 911(g)(4) to take into account many factors, including “the increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product.” Although at the time the Family Smoking Prevention and Tobacco Control Act (FSPTCA) was enacted, e-cigarettes were not a significant

consideration and were not under the jurisdiction of the FDA, today any serious consideration of the impact on “existing tobacco product users” must necessarily consider e-cigarette users.

If it is determined that e-cigarettes are less harmful than IQOS, an existing e-cigarette user who switches to IQOS would actually *increase* their harm and the risk of tobacco-related disease, rather than “significantly reduce harm and the risk of tobacco-related disease.” Indeed, this seems likely considering e-cigarettes do not contain actual tobacco leaf (although they contain nicotine derived from tobacco) and the e-liquid is typically heated to 400 degrees F as compared with 650 degrees F for IQOS.

Page 26, figure 4: Although just a schematic, the assumption here is that the effects of changing exposures is linear. Many of the effects, particularly for cardiovascular disease, are highly nonlinear, with big effects occurring in low levels of exposure. There may be similar evidence for some pulmonary outcomes.

Page 27, paragraph 1: It is important to consider the independence and integrity of the people who wrote the papers upon which PMI’s application relies. Peter N. Lee, while represented as an “independent statistical consultant,” has a longtime association with Philip Morris, British American Tobacco, the Tobacco Institute, and the tobacco industry in general. It is possible that some or all of the other authors, whose credentials appear to be independent statisticians and epidemiologists, may also be either employed by the industry or industry apologists.

Page 29, item A, III: Here PMI is just comparing the toxins in IQOS aerosol with cigarette smoke. Given the differences in the construction of the IQOS heat sticks compared to a conventional cigarette, there is a strong possibility that it will have a different toxicological profile that includes elements that may not be present in cigarette smoke. Complete assessment of the toxicity of the product would require looking beyond cigarettes.

Page 30, Table 1, B, Step (7): PMI’s post-market surveillance includes “cross-sectional surveys to monitor prevalence and cohort studies to monitor the ongoing health effects of switching to THS.” This presumes that the only behavior will be switching. It is also very important to monitor dual use, youth initiation and relapse among former smokers.

When determining whether the candidate product benefits the health of individuals and the population as a whole, FDA is required under section 911(g)(4) to take into account “the increased or decreased likelihood that persons who do not use tobacco products [including youth who have not yet begun smoking and former smokers who had quit smoking] will start using the tobacco product that is the subject of the application.” These groups also would need to be monitored post-market, as well as carefully scrutinized before FDA may issue a MRTP order.

Page 31, paragraph 1: All the comparisons are against 3R4F research cigarettes. The comparisons should be made against Marlboros, since those are the cigarettes which are currently being used in the market. Moreover, this is particularly important for this application because the new IQOS will be co-branded with Marlboro.

Page 32, paragraph 3: The International Conference on Harmonization (ICH) works closely with industry to influence regulators to accelerate review times and minimize the regulatory

process for new products (<https://fda.gov/downloads/Drugs/NewsEvents/UCM446914.pdf>). It is therefore questionable for FDA to rely on recommendations made by the ICH when considering the health consequences of IQOS and PMI's MRTP application.

Page 33, paragraph 2: “The PMI list of analytes and constituents does not cover the components of flavor systems.” Flavors should not have been excluded. Flavors are an important part of all tobacco products, and especially of the new IQOS. Two of the three product variants for which PMI seeks MRTP marketing orders are flavored products: Marlboro Smooth Menthol HeatSticks, and Marlboro Fresh Menthol HeatSticks. The fact that PMI created two different variants of just one flavor – menthol – further highlights the importance of flavors to PMI's product profiles.

Page 34, second bullet: Philip Morris sets the goal of assessing the aerosol particle size to confirm that the aerosol is respirable. It is also important to investigate if the particles are smaller, and hence more dangerous, than particles generated in cigarette smoke. This is the case for many e-cigarettes.

Page 35, top two lines: “PMI chose to include those 18 HPHCs in its testing protocols along with additional analytes [that fulfilled certain criteria].” Why did PMI leave the others out and what is the impact of leaving these out? PMI should also be screening for biologically important toxins outside this list because IQOS are not conventional cigarettes and likely have a different toxicological profile.

Page 36, table 2: This table shows that neither nicotine free dry particulate matter nor total particulate matter are associated with any health risks. This is clearly incorrect.

Page 45, second paragraph: The nicotine exposure level that PMI used as a benchmark comes from the Occupational Safety and Health Administration. This is a level of occupational exposures which are substantially higher than would be considered acceptable as an environmental exposure in the general population.

Page 45, last paragraph: How accurate are the neutral red uptake assay, the Ames bacterial mutagenicity assay, and the mouse lymphoma mammalian mutant indigenous city assay for determining dose response, as opposed to simply identifying toxins as positive or negative?

Page 53, clinical pathology parameters: How does the fact that the IQOS line simply falls along the same line as for conventional cigarettes for blood neutrophil counts and alkylene phosphatase activity indicate reduced risk?

Page 53, histopathology of the respiratory tract: The changes observed in the respiratory tract (reserve cell hyperplasia and respiratory epithelium) and the nasal cavity (nose level I) in female rats exposed to IQOS aerosol are about half that of conventional cigarettes.

Page 54, hyperplasia, arythenoid projections: The changes observed in the larynx (hyperplasia, arythenoid projections) in female rats exposed to IQOS aerosol are about half that of conventional cigarettes.

Page 75, third paragraph: While dual use of IQOS and conventional cigarettes was not allowed during the confinement studies, it was only “discouraged” during the ambulatory period of the study. The results of the study, presented later, show substantial levels of dual use.

Page 91, table 10: These two studies measuring oxidative stress reveal that **there is no statistically significant difference between IQOS and conventional cigarettes** for the clinical risk endpoint 8-epi-PGF2 α .

Page 92, table 11: These two studies measuring platelet activation reveal **there is no statistically significant difference between IQOS and conventional cigarettes** for the clinical risk endpoint 11-DCTX-B2. Even Philip Morris acknowledged at the bottom of page 91 that “the magnitude of the change is smaller than expected.” However, they failed to point out that it was not a statistically significant change.

Page 94, table 12: The difference in FEV₁ between IQOS and conventional cigarettes is not significantly different from zero.

Page 95, table 13: The difference between IQOS and conventional cigarettes for HDL-cholesterol was not statistically significant.

Page 96, table 14: The difference in white blood cell counts between IQOS and conventional cigarettes was not statistically significant.

Page 97, table 15: There was a statistically significant drop in sICAM-1 in IQOS users compared to conventional cigarettes. This is a measure of endothelial function. Of all the clinical endpoints that PMI measured in people, this was the only statistically significant improvement associated with IQOS. Given that PMI did 24 tests, one would expect 1 false positive, so this is likely to be a chance finding.

Page 97, summary of clinical endpoints: “In summary, 90 days after switching from menthol cigarette smoking to menthol THS use, there was a shift in the same direction for all (except WBC in the US study) of the clinical risk endpoints.” While this is a true statement, it ignores the fact that *all but one of these shifts was not statistically significant*.

The failure to document statistically significant improvements in these biomarkers raises serious questions about any claims of reduced risk associated with IQOS. While Philip Morris’s data does show that there are reductions in several measures in isolated cell systems and even animals, *failure to reach significance in humans is a serious problem* and trumps all of the lower level data. There are many examples of clinical interventions which look promising in *in vitro* studies or even animals that ended up not working in people. *The data Philip Morris presents in this application is consistent with that larger pattern and calls into question any reduced risk claims that might be made.*

Moreover, the fact that there is not actual reduced risk in people suggests that approving any reduced exposure claims could be fundamentally misleading because consumers would

inevitably read the claim of reduced exposure as equating to reduced risk. Section 911(g)(2)(B) is crystal clear on this point: To issue a reduced risk order, FDA must “find that the applicant has demonstrated that... (iii) *testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product (I) is or has been demonstrated to be less harmful* [emphasis added].” FDA’s Guidance on MRTP applications admonishes applicants to submit specific kinds of scientific studies concerning consumer perception and understanding that should inform FDA’s evaluation. PMI has failed to meet this burden.

Page 98, paragraph 1: “The shifts in the clinical risk endpoints of smokers who switched to mTHS were of similar magnitude to those seen following 90 days of smoking abstinence. Therefore, PMI has met its objectives for Evidence Level IV (Reduced Exposure and Risk).” PMI may have met its own objectives, but no reasonable independent reader would agree that they have made a convincing case that switching to IQOS actually reduced risks.

As noted above, except for one outcome (which is likely a chance finding), there was not a statistically significant improvement in the biomarkers that PMI examined. In addition, the statement as worded suggests that the effects were the same or comparable to the effects of smoking cessation. Looking at the table shows that the point estimates of the effects of smoking cessation were always larger than the point estimates associated with using IQOS.

Page 113-114, perception and behavior assessment (PBA) framework: Nothing in this framework discusses effects on kids, a very serious omission.

Page 114, first full paragraph: “...PMI built its premarket PBA program leveraging on available best practice guidelines related to other categories than tobacco, such as Over-the-Counter drugs.” There is no justification for doing this since there are no therapeutic benefits associated with IQOS. A more appropriate standard to use would be best practices in tobacco control as embodied in the Framework Convention on Tobacco Control and CDC best practices for tobacco control.

Page 117, bullet points: Again, nothing in this analysis discusses effects on kids.

Page 119, item 2: The whole model begins with young adult non-smokers of legal age through 25; however, it completely fails to consider kids, who are likely to be substantially affected by the existence of this new product.

Page 120, paragraph 3: It would be useful to have more details about these inserts and onserts since research that UCSF researchers have been doing in the industry documents clearly indicates that Philip Morris knows how to prepare such materials so that they will or purposefully will not effectively communicate.

Page 120, paragraph 4: Again, this analysis contains no mention of kids.

Page 126: An important question which PMI completely ignores in this analysis is how the existence of IQOS will affect kids starting IQOS and how that will relate to their smoking

initiation and cessation behavior later. What about the possibility that kids, thinking IQOS is safe, will initiate with cigarettes figuring that they can later switched IQOS just as they often think that they can later simply quit smoking? These are important population level of facts which are completely ignored in the analysis.

Sections 911 (g)(1)(B), 911(g)(2)(B)(iv), and 911(g)(4)(C) and FDA's Guidance are unambiguous on the point that *all MRTP applications must consider the effect on tobacco use initiation among non-users, which necessarily includes kids*. The Guidance states at page 20, "*A critical population health consideration* under section 911(g)(1)(B) and 911(g)(2)(B)(iv) of the FD&C is the effect that an MRTP and its marketing will have on tobacco use initiation among non-users (both never users and former users). *An MRTPA must contain scientific evidence regarding the effect the product and its marketing will have on increasing the likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application.* [emphasis added]." Because PMI failed to provide this critical evidence, the law requires FDA to deny its MRTP application.

Page 128, first bullet in the second set of bullets: PMI defines "exclusive THS use" as IQOS consisting of at least 70% of total tobacco usage. This means that someone who is consuming 30% of their total tobacco product use as conventional cigarettes would be counted as having "completely switched" IQOS. These people would much more reasonably considered dual users. Philip Morris gives no breakdown of the distribution of use between IQOS and conventional cigarettes in this group. Given that Philip Morris makes such a big deal out of the benefits of *switching completely* from cigarettes to IQOS, it is very misleading to count people who are still consuming 30% of their tobacco use with conventional cigarettes as having "completely switched." This definition masks a lot of dual use in all of the subsequent analysis and needs to be corrected so that switchers are indeed 100% switchers.

Additionally, section 911(h)(3)(B) provides that FDA may require that the labeling of a proposed MRTP product include the conditions of use "if the conditions of use of the tobacco product may affect the risk of the product to human health." PMI has not provided the required showing that the labeling of IQOS clearly or effectively communicates that a condition of use for the product is to switch completely from conventional cigarettes, nor does PMI demonstrate that consumers understand that they need to switch completely to IQOS to get the purported benefits.

Page 129, first bullet: The 70% cut off for "exclusive use" is used again here.

Page 135, table 25: This table invites the question, how many of the people presented in this table would be attracted to IQOS instead of simply quitting smoking entirely? This is an important question which PMI's application ignores. Importantly, section 911(g)(4)(B) *requires* FDA to take into account "the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to [IQOS]."

Page 136, table 26: The same comment applies to this table. PMI should have compared with people who would have just quit smoking.

Page 137, figure 28: Is either number of former smokers who have a positive attitude toward intending to use IQOS high enough to matter? PMI fails to compare this number with normal relapse rates in long-term former smokers.

Page 138, first full paragraph: While Philip Morris talks about “intentions to quit,” what does “quit” mean? Does it mean stopping using nicotine products entirely, or stopping conventional cigarettes and switching to IQOS? This is an important consideration that FDA is required to consider under section 911(g)(4)(B).

Page 140, top bullet: “Adult Smokers with the Intention to Quit smoking did not substantially change their intention to quit smoking and the use of tobacco products even though they expressed interest in the trial and use of THS [IQOS].” An alternative explanation of the data would be that the changes were consistently associated in the direction of lower intent to quit being associated with the availability of IQOS.

Page 140, third to last paragraph: PMI failed to explain the consequences of so many consumers using the product incorrectly.

Page 141, last paragraph: This is another place where “complete substitution” is considered people who use IQOS for 70-100% of their total product usage. This includes a lot of dual users; as many as 30% of so-called “complete switchers” are using other tobacco products, including convention cigarettes, using PMI’s own figures. Given that PMI makes such a big deal out of the benefits of complete substitution of IQOS for conventional cigarettes in their health effects modeling, the behavioral data should explicitly present what fraction of users have completely switched. PMI also needs to explore the health effects of dual use, which is high.

Page 142, figure 31: It is important to note that Philip Morris did collect data where “exclusive use” is defined as 95% or more IQOS use, so they obviously have thought about this issue. But, except for the Japanese study, they used the 70% cut off in the right-hand part of this figure. For the reasons stated above, this is at the very least misleading.

Page 144, figure 33: This figure does not make clear whether the THS consumers smoke any conventional cigarettes during the 90 days.

Page 144, second paragraph: Philip Morris makes the point that subjects were highly compliant to their assigned product in the Japanese study. But, “during the ambulatory period, 91% of the subjects used mTHS. Eighty-two percent of these subjects used mTHS 100% of the time throughout the 85 days in the ambulatory period.” *This means that 18% were dual users or went back to conventional cigarettes. That’s a big effect.*

Page 146, bottom: The fact that “THS delivers nicotine to the users at comparable levels compared with cigarettes” means that THS has the same addictive potential and abuse liability, which is a direct consequence of the statements at the beginning of page 147.

Page 147, figure 35: This figure shows that even using Philip Morris’s loose definition of “complete conversion” to IQOS ($\geq 70\%$ of total tobacco consumption), 22.4% of users are dual users at the end of six weeks. And that does not account for what fraction of the 14.6% who are counted as converters are actually dual users. *This is a substantial level of dual use, which points to the importance of assessing the health effects of dual use.*

Page 148, first paragraph: It is not obvious from the graph that this statement is correct. Some of the people can switch back to conventional cigarettes.

Page 148, last paragraph: “In summary, this study showed that approximately 15% of the participants were able to switch from cigarettes to THS and to adopt it as a substitute for cigarettes.” As noted above, PMI’s loose definition of “substitution” draws this statement into question. This could easily be read as saying that these people converted completely from conventional cigarettes to IQOS, when in fact many of them were still dual users with conventional cigarettes.

Page 149, figure 36: This chart, looking across several countries, shows that dual use is a substantial behavior. Using PMI’s definition of dual use (the tan areas on the graph) approximately 30 to 50% of users are dual users. In addition, as noted above, many of the people identified as converters to IQOS (the blue bars) only represent 70% conversion, so many of these people are probably also dual users.

Page 149, first sentence: “The results of the WOTs show that between 10% and 37% of adult daily smokers, depending on the country, were able to adopt THS as *a substitute* to their cigarettes [emphasis added].” For the reasons discussed above, this is an inaccurate statement, since the data do not present the numbers for complete substitution.

Page 150, second paragraph: It is not clear what the 4.1% figure is a percentage of. Is it IQOS users and smokers? The fact that by mid-September the IQOS market share in Japan reached 4.1% in a situation where the ratio of the number of IQOS devices and the estimated number of Japanese adult smokers was 9.5% suggests that about half the IQOS users were still dual using the cigarettes.

Page 150, last paragraph: The Market Research Panel panel that PMI established in Japan “include only adult IQOS purchasers who registered their device in a PMI database, and who agree to participate.” As PMI notes in the next sentence, “due to this potential selection bias, the panel presents some limitations in the generalizability of the findings.” This limitation is very important in interpreting the subsequent results because the biases that Philip Morris identifies are almost certainly substantial, which can lead to an overestimate of IQOS use and probably an underestimate of dual use. This limitation, which PMI recognizes, needs to be kept in mind in interpreting all of the results from this database.

Page 151, figure 38: It is important to note that in this figure the exclusive IQOS users are defined as those people who use IQOS for 95% or more of their tobacco consumption. This is a more reasonable definition of exclusive users than the 70% used in all the other studies. Even with this more stringent definition, however, about 30% of the users in the Philip Morris Japan

Registry are dual users. (See previous note on the biases that are built into the way the registry was created.)

Page 152, middle of first paragraph: “The repeated exposure to various forms of communication facilitates adoption among adult smokers, not only by those who are usually the first to try innovative products (“innovators”) but also by those who tend to adopt products when they have become more generally acceptable.” As PMI says, the panel is likely biased toward IQOS enthusiasts. Even so, about 50% are dual users.

Page 153, first paragraph: “This suggests that, once converted and IQOS use becomes familiar, the adoption of the new ritual and satisfactory experience seems to prevent IQOS users from switching back to other tobacco products. IQOS users who are in a “situational” status have a similar probability to either convert or remain in the same category and continue to use IQOS in conjunction with other tobacco products (51.9% and 41.6% respectively for May 2016 cohort).” In interpreting these numbers, it is important to remember that the biases built into the Japanese sample could be seriously affecting these estimates compared to the general population.

Page 154, figure 41: These transition probabilities are biased toward IQOS only use because of the difficulties with the Japanese registry sample discussed above.

Page 154, second paragraph: 1.2% initiation among adult never smokers is a lot of initiation among adults.

Page 155, second line: Based on the discussion earlier, it is not clear that the data support the conclusion that “the rate of initiation and relapse associated with IQOS commercial availability are very low.” This statement is based on the biased (by PMI’s own admission) Japanese registry.

Page 159, figure 45: This figure seems to show that if people quit smoking after about 30 days, their cravings are lower than if they use the IQOS product or continue smoking. Does this raise the possibility that the existence of IQOS would further discourage smoking cessation? FDA is required by law to consider this possibility, and if it determines that IQOS would discourage cessation, it should deny PMI’s MRTP application.

Page 159, first paragraph: “Second, THS does not deliver additional addictive substances compared with cigarettes.” This raises the interesting question of what other additional addictive substances cigarettes deliver beyond nicotine.

Page 159, second paragraph: “Based on the totality of the available evidence, THS has a similar abuse liability than cigarettes and there is no significant evidence that THS is attractive to non-users of tobacco.” Nothing in the report so far shows that this is true because Philip Morris did not look at kids. Most smokers start smoking before age 18, and this group of people were systematically excluded from this work.

Page 160, first paragraph: The logical conclusion of this paragraph is that THS has the same abuse liability as a cigarette.

Page 160, second paragraph: “Results on product consumption and use patterns, both in controlled as well as in near real-world conditions, suggest that THS is likely to be adopted by current cigarette smokers.” This is overstated.

Page 160, second paragraph: “Furthermore, smokers who switch to THS do not increase their overall tobacco consumption, and most studies demonstrated that total tobacco consumption actually decreased in those smokers who completely switched to THS.” It is not clear where PMI showed this in the Executive Summary.

Page 160, third paragraph: “...the level of THS consumption tended to stabilize to reach levels comparable to what was reported at baseline for cigarettes.” It is not clear where PMI showed this in the Executive Summary. Moreover, this statement contradicts the statement made in the paragraph above just commented on.

Page 160, paragraph 4: “The PBA study data on the THS messages consistently demonstrated that the product messages generated substantial Intent to Use THS among adult smokers including smokers with the intention to quit smoking. However, the data also shows that nine out of ten smokers who expressed an intention to quit stated that THS did not change their overall intentions.” That leaves the other 10%, who may have been discouraged from quitting.

Page 161, paragraph 3: Again, this does not include kids.

Page 161, last paragraph: The study in question only involved 30 adult former smokers and six adult never smokers, which puts Philip Morris in the position of drawing very small conclusions based on extremely small sample sizes.

Page 163, second paragraph: “Among Adult Former Smokers, across all THS messages, positive Intention to Try ranged from 0% to 4.2% and positive Intention to Use from 4.1% to 15.7%.” It is important to recognize that 4.2% is a big number if you are talking about encouraging people who previously quit smoking to take up THS. Likewise, having a 6% intention to use THS among young adult former smokers is also quite high.

Page 163 third paragraph: The statement that “all three studies [references omitted] confirmed a consistent low or very low Intention to Use THS among adult non-smokers” is an overstatement affecting 4 to 6% of these adult former smokers, which is significant.

Page 163, third paragraph: Saying that 9.6% of Adult Former Smokers expressed a positive Intention to Try is a lot of people, even though Philip Morris characterizes this as being “in the low single digits.” That 5.3% of these smokers also expressed an Intention to Use of 5.3% is also a lot.

Page 164, table 29: All these percentages are based on very small numbers.

Page 164, last paragraph: “Furthermore, the propensity to initiate with THS is not significantly different from that of initiating with a comparator product (cigarettes or e-cigarettes). In addition,

young adult LA-25 never smokers (LA-25) appeared to have the same or even lower interest in product trial and use than Adult Never Smokers in general. Taken together, all these results indicate that THS is not likely to increase tobacco use at the population level.” ***There is no way that PMI can make the statements without information about kids,² which is the main group that initiates tobacco use. Kids are also the group in which e-cigarette use has penetrated the market most, not adult smokers.***

Page 165, first paragraph: “Whereas a commercial MRTP could be of benefit to the smokers who switch completely from cigarettes, it could also have a negative impact on the population as a whole by encouraging nonsmokers to start using a tobacco product or alter the decision of current smokers who intend to quit either smoking or the use of all tobacco products.” This statement ignores the possibilities of dual use, which would also have negative health effects. Moreover, this is another example of a sweeping statement made in the face of ignoring the effects of IQOS on youth.

Page 165, last paragraph: The studies about comprehension of the warning labels did not address the issue of reading level at all. What evidence has Philip Morris’s presented that the reading level of these warnings is comparable to the typical smoker who is less educated than the population on the average? Also, Philip Morris did not do any studies of how these warning labels are perceived by kids. What about non-English speakers? PMI and other tobacco companies advertise in languages other than English; they should also warn in these other languages.

Page 166, figure 46: PMI did not address the question of how many of these people understood the warning labels as indicating that IQOS was “safe.” This is something that is important to test and report as part of the MRTP application. Indeed, section 911(g)(2)(B)(iii) requires that to issue an MRTP order, FDA must find that PMI demonstrated that “testing of actual consumer perception shows that, as [PMI] proposed to label and market [IQOS], consumers will not be misled into believing that [IQOS] is or has been demonstrated to be less harmful...” As stated above, PMI has also failed to demonstrate that consumers understand that to attain the purported benefits of IQOS, they would have to switch completely from cigarettes to IQOS.

Page 167, second paragraph: These statements all ignore the effects that could encourage kids to use the product.

Page 168 second paragraph: The information here ignores the question of how many people would interpret these warnings as indicating that IQOS is “safe.”

Page 169, first paragraph: This is another place where PMI talks about brochures on the Heat Stick pack and in direct mail communications, but does not really provide much information about the nature of these communications. FDA needs to pay particular attention to whether PMI’s proposed materials are presented in a way that would both attract attention and be read and comprehended by consumers.

² Neither PMI nor any other tobacco company should be permitted to conduct, directly or indirectly, studies on kids because of the high risk that the resulting information will be used to sell their products to kids. PMI should rely on research conducted completely independent of the tobacco industry.

Page 170, both paragraphs: PMI failed to analyze issues of nonlinear dose-response, where the reduction in risk is not proportional to the reduction in exposure. In addition, given that Philip Morris's data in general shows no significant reduction in biomarkers of harm in actual people, it seems that presenting information on reduced exposure would be inappropriate or even misleading. Simply presenting information on exposure level is what you would do if you did not have any information about biological activity at all, or at least not in humans.

Page 173, bullets at the bottom: Again, there is no information at all here relating to kids.

Page 174, paragraph 1: "There are some challenges presented by reduced risk versus reduced exposure claim, primarily based on the finding that consumers believe that a reduction in exposure leads to a reduction in risk of harm and tobacco-related disease. PMI has demonstrated this to be true." *This a very important statement because it has Philip Morris recognizing that reduced exposure claims are interpreted as reduced harm claims.* As noted above, however, even though Philip Morris presents data on reduced exposure, the human data generally does not show reduced harm. *For the reasons that Philip Morris points out, they should not be allowed to make reduced exposure claims because they would be fundamentally misleading to the readers.*

This is in many ways a legal issue, but it is informed by the labeling issue. Really depends on consumer perceptions and understanding of the labels, labeling, and marketing (PMI calls this "LLM"), and needs to be addressed. Even if PMI could prove reduced health harms and/or reduced exposure claims, this is not enough if the labels are misleading or downright deceptive. Bonnie's input is key here. See Chapter 6.4 and FDA guidance for more details.

Page 174, paragraph 5: The statements about overall population levels of harm completely ignore the effects on kids. The summary statement also ignores the implications of the high levels of dual use documented in the work and does not adequately address the risk of relapse to smoking among people who would otherwise quit.

Page 176, bottom: The epidemiological risk compounding in the model is all based on reductions of exposure, not risk. As noted above, Philip Morris's own data show that despite substantial reductions in exposure, there is generally not a statistically significant reduction in biomarkers of risk in human beings.

Page 179, paragraph 2: This scenario is ridiculous because it is based on highly questionable assumptions.

Page 180, all the text: There is nothing in the model to account for new youth smokers being attracted to use IQOS.

Page 181, first paragraph: The statement that there would only be 2% dual users is inconsistent with the data presented in this report. Dual use is much higher than that.

Page 182, figure 55: There is no mention of effects on youth in the initiation/cessation use patterns part of their post-marketing surveillance.

Page 183, cross-sectional surveys: There is no mention of collecting data in kids, which as noted above, are a very important part of the population in terms of overall population impact. (As noted above, such data would need to be collected completely independent of PMI or any other tobacco company or affiliated unit.)

Page 190, items 6 and 7: Philip Morris states that their studies have shown “significantly reduced exposure to HPHCs,” which is accurate. In item 7, however, they only say that “clinical studies have shown that switching from cigarette smoking to THS results in *positive changes* in clinical risk markers that are similar to those seen following smoking cessation [emphasis added].” This statement is misleading on two counts. First, unlike the changes in exposure, the changes in clinical risk markers were *not statistically significant*. Second, while the point estimates were in the direction toward smoking cessation, they were not as large a change as were observed with smoking cessation. Someone reading this statement quickly or who is not familiar with the nuances of statistical significance versus just a change in the point estimate could easily misread this statement to indicate that there were statistically significant benefits both in terms of reduced exposure and also reduced clinical risk markers. That is not what the data show.